



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>5</sup> :  C07D 401/04, A61K 31/44</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 92/06085</b>  (43) International Publication Date: 16 April 1992 (16.04.92)</p>
<p>(21) International Application Number: PCT/GB91/01663 (22) International Filing Date: 26 September 1991 (26.09.91)  (30) Priority data: 9021184.8 28 September 1990 (28.09.90) GB 9117657.8 15 August 1991 (15.08.91) GB  (71) Applicant (for all designated States except US): SMITH KLINE &amp; FRENCH LABORATORIES LIMITED [GB/GB]; Mundells, Welwin Garden City, Hertfordshire AL7 1EY (GB).  (72) Inventors; and (75) Inventors/Applicants (for US only) : PORTER, Roderick, Alan [GB/GB]; MURRAY, Kenneth, John [GB/GB]; WARRINGTON, Brian, Herbert [GB/GB]; PRAIN, Hunter, Douglas [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).</p>		<p>(74) Agent: THOMPSON, Clive, B.; Corporate Patents, Smith-Kline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).  (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: PHENYLPYRIDINOL DERIVATIVES AS MEDICAMENTS

(57) Abstract

Phenylpyridinol derivatives are disclosed as medicaments.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU <sup>+</sup>	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

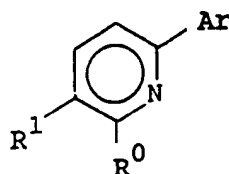
<sup>+</sup> Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

PHENYLPYRIDINOL DERIVATIVES  
AS MEDICAMENTS

The present invention relates to pyridinol derivatives, processes for their preparation, intermediates in their preparation, their use as medicaments and to pharmaceutical compositions comprising them.

The compounds of this invention are agonists of a cyclic AMP-dependent protein kinase (cA-PrK) (see J. Biol. Chem., 1989, 264, 8443 - 8446) and are of use in combatting such conditions where such agonism is thought to be beneficial. They are likely to have anti-proliferative, anti-aggregatory, cholesterol-lowering, smooth muscle relaxant, lusitropic, anti-allergic or anti-inflammatory activities. They are likely to be useful in the treatment of cardiovascular diseases such as congestive heart-failure, cancer, psoriasis, atherosclerosis, thrombosis, chronic reversible lung disease such as asthma and bronchitis, allergic disease such as allergic asthma, allergic rhinitis and urticaria or gut motility disorders such as irritable bowel syndrome.

Accordingly the present invention provides compounds of the formula (1) :



(1)

or pharmaceutically acceptable salts thereof, wherein :

- 2 -

$R^0$  is OH or a bioprecursor thereof,  
 $R^1$  is 5-tetrazolyl or a bioprecursor thereof, and  
Ar is phenyl substituted by one to three groups independently  
selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{1-6}$ alkoxy,  
5  $C_{3-6}$ alkenyloxy,  $C_{3-6}$ cycloalkyl,  $C_{3-6}$ cycloalkoxy,  
 $C_{1-6}$ alkylthio, phenyl, phenylthio, benzyloxy,  
 $C_{1-6}$ polyfluoroalkyl,  $C_{1-6}$ polyfluoroalkoxy, halo,  $NR_2$ , or  
NHCOR wherein R is H or  $C_{1-6}$ alkyl, or  $-X(CH_2)_nY-$   
attached to adjacent carbon atoms of the phenyl ring wherein X  
10 and Y are independently  $CH_2$  or O and n is 1 to 3, wherein  
said  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl or  $C_{1-6}$ alkoxy groups can be  
independently substituted by OH,  $C_{1-6}$ alkoxy,  
 $C_{3-6}$ cycloalkyl,  $NR_2$ ,  $CO_2R$  or  $CONR_2$ ; with the proviso  
that Ar is not phenyl monosubstituted by 2- $C_{1-6}$ alkoxy.

15

Bioprecursors of the group  $R^0$  are derivatives thereof  
which are convertible in vivo into the group  $R^0$ .

A suitable bioprecursor of the group  $R^0$  is  $OR^2$  wherein  
20  $R^2$  is  $C_{1-4}$ alkyl, aryl $C_{1-4}$ alkyl (for example phenyl $C_{1-4}$ -  
alkyl such as benzyl),  $C_{1-4}$ alkanoyl (for example acetyl),  
aryl $C_{1-4}$ alkanoyl (for example phenyl  $C_{1-4}$ alkanoyl such as  
benzoyl), arylsulphonyl (for example optionally substituted  
phenylsulphonyl or toluenesulphonyl) or  $C_{1-4}$ alkylsulphonyl  
25 (for example methylsulphonyl).

Suitably  $R^0$  is hydroxy or  $OR^2$ , preferably hydroxy.

A suitable bioprecursor of  $R^1$  is a N-protected  
30 tetrazolyl group. Suitable N-protecting groups include  
pivaloxyloxymethyl, propionyloxymethyl and  
pivaloxyloxycarbonyloxymethyl.

- 3 -

By the term alkyl is meant both straight- and branched-chain alkyl.

By the term C<sub>1-6</sub> polyfluoroalkyl is meant a C<sub>1-6</sub>alkyl group having at least one hydrogen replaced with fluoro eg. CF<sub>3</sub>, or CF<sub>2</sub>CF<sub>2</sub>H.

Suitably Ar is phenyl mono-substituted by a group as hereinbefore defined, for example in the 2,3, or 4 positions by C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyloxy, C<sub>1-6</sub>alkylthio, phenyl, phenylthio, benzyloxy, CF<sub>3</sub>, halo or NHCOR, or in the 3, or 4-positions with C<sub>1-6</sub>alkoxy.

Suitably Ar is phenyl di-substituted by any groups as hereinbefore defined, for example in the 3,4-, 3,5-, 2,3-, 2,4- or 2,5-, positions by groups independently selected from C<sub>2-6</sub>alkenyl, C<sub>1-6</sub>alkoxy, C<sub>3-6</sub>cycloalkoxy, halo, -X(CH<sub>2</sub>)<sub>n</sub>Y- or C<sub>1-6</sub>alkoxy.

Suitably Ar is phenyl trisubstituted by any groups as hereinbefore defined, for example in the 2,3,4-, 2,3,5-, or 3,4,5-positions by groups independently selected from C<sub>2-6</sub>alkenyl, C<sub>1-6</sub>alkoxy or halo.

Examples of C<sub>1-6</sub>alkoxy include methoxy, ethoxy, propoxy, butoxy, or pentyloxy.

Examples of C<sub>1-6</sub>alkyl include methyl, ethyl, propyl, butyl, isobutyl or pentyl.

Examples of halo include fluoro, chloro, bromo or iodo, preferably chloro or bromo.

35

Particular compounds of this invention include :

- 4 -

- 6-(3-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 5 6-(3-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3-butoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 10 6-(3-benzyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3-bromophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 15 6-(3-trifluoromethyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3-ethylphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 20 6-(4-butoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 25 6-(4-isobutylphenyl)pyridin-2(1H)-one,
- 6-(4-biphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 30 6-(4-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(4-methoxy-3-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

- 5 -

- 6-(3,4-methylenedioxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 5 6-(3,4-dichlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3,5-dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 10 6-(3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3,5-dibromophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 15 6-(2,4-dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(2,5-dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 20 6-(2,3,4-trichlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 25 6-[6-(1,2,3,4-tetrahydronaphthyl)]-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3-chlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 30 6-(3-phenylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 3,4-dimethoxyphenyl-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 35

- 6 -

- 6-(3-methylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 5 6-(3-butylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3,4-di-n-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 10 6-(2,3-di-n-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3-cyclopentyloxy-4-methoxyphenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one
- 15 6-(3-ethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3,5-dimethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 20 6-(2-butylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 25 6-(3-allyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(4-methoxy-2-pentyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one
- 30 6-(3-iso-butoxy-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 35 6-(2-bromo-3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

- 7 -

- 6-(5-bromo-4-methoxy-2-pentyloxyphenyl)-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,
- 5 6-(2-allyl-4-methoxy-3-propoxyphenyl)-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,
- 6-[3-(E-1-propenyl)-4-methoxyphenyl]-3-(5-tetrazolyl)pyridi  
n-2(1H)-one,
- 10 6-(4-methoxy-3-propoxyphenyl)-3-[5-(1-pivaloyloxymethyl)-  
tetrazolyl]pyridin-2(1H)-one,
- 6-(4-methoxy-3-propoxyphenyl)-3-[5-(2-pivaloyloxymethyl)-  
tetrazolyl]pyridin-2(1H)-one,
- 15 6-[3-ethoxy-5-(2-methoxyethoxy)phenyl]-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,
- 6-[3-(2,2-dimethylpropyloxy)-4-methoxyphenyl]-3-(5-  
20 tetrazolyl)pyridin-2(1H)-one,
- 6-(3-ethoxy-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-  
one,
- 25 6-(3-propionamidophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(4-methoxy-3-propylphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-  
one,
- 30 6-(3-bromo-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-  
one,
- 6-(3-phenyl-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-  
35 one,

- 8 -

6-[4-methoxy-3,5-di(E-1-propenyl)phenyl]-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,

5 6-[3-(E-1-propenyl)-4-propoxyphenyl]-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,

6-(3-bromo-4-methoxy-5-propylphenyl)-3-(5-tetrazolyl)-  
pyridin-2-(1H)-one,

10 6-(2-butylthio-3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-  
2(1H)-one,

15 6-(3-bromo-4-N,N-dimethylaminophenyl)-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,

6-(3-acetamido-4-methoxy-5-propylphenyl)-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,

20 6-[3-methoxymethyl-4-methoxy-5-(E-1-propenyl)phenyl]-3-(5-  
tetrazolyl)pyridin-2(1H)-one,

25 6-[3-(E-2-carbamoylethenyl)-4-methoxy-5-(E-1-propenyl)-  
phenyl]-3-(5-tetrazolyl)pyridin-2-(1H)-one, and

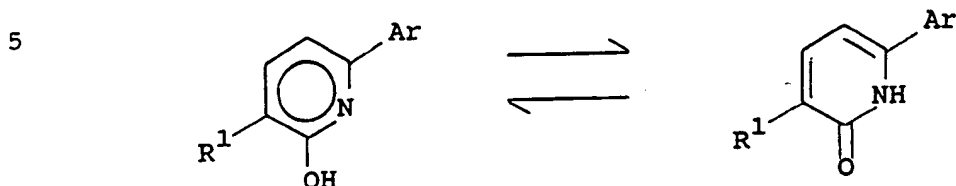
6-(3-cyclopropylmethyloxy-4-methoxyphenyl)pyridin-2(1H)-one

and pharmaceutically acceptable salts thereof.

30 This invention covers all tautcmeric, geometric and  
optical isomeric forms of compounds of formula (1). In

- 9 -

particular when  $R^0$  is hydroxy the compound can exist in its keto tautomeric form :



Compounds of the formula (1) can form pharmaceutically acceptable base addition salts with metal ions, such as alkali metals for example sodium or potassium, or with an ammonium ion.

15

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

20

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

25

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the

30

35

- 10 -

composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose, sucrose and magnesium stearate.

- 5 Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used  
10 for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

- 15 Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, lecithin,  
20 2-pyrrolidone, cyclodextrin, arachis oil, or sesame oil.

- A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this  
25 way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

- 30 Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

- 35 Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered

- 11 -

in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

5            Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

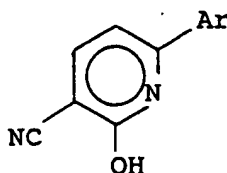
10           Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the  
15           free acid.

            The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof  
20           calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The  
25           active ingredient may be administered as required for example from 1 - 8 times a day or by infusion. The compositions of the invention are agonists of a cA-PrK and are of use in combatting such conditions where such agonism is thought to be beneficial. Such conditions can  
30           be treated by administration orally, sublingually topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1 - 5.0 mg of a compound of  
35           the formula (1) or a pharmaceutically acceptable salt thereof.

- 12 -

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a single pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H<sub>1</sub>-antagonists, drugs used in the treatment of cancer such as those which inhibit the synthesis of or inactivate DNA, for example methotrexate, fluoracil, cisplatin, actinomycin D, anti-atherosclerotic agents for example cholesterol lowering drugs such as HMGCoA reductase inhibitors, bile acid sequestrants, drugs for the treatment of psoriasis, for example retinoids, anthralin, anti-inflammatories for example corticosteroids, non-steroid anti-inflammatories such as aspirin, antithrombotics for example dipyridamole, or fibrinolytic agents.

In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises reacting a compound of the formula (2) :



(2)

- 13 -

wherein Ar is as hereinbefore defined with an azide salt,  
and optionally thereafter :

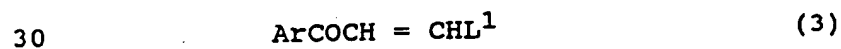
- forming a bioprecursor of  $R^0$  and/or  $R^1$
- 5 • forming a pharmaceutically acceptable salt.

A compound of the formula (2) is suitably reacted  
with an azide salt such as ammonium, sodium, potassium or  
10 aluminium azide in an organic solvent such as  
dimethylformamide, dimethylsulphoxide, N-methyl-  
pyrrolidone or tetrahydrofuran at an elevated temperature  
e.g. 40 - 200°C, preferably at the reflux temperature of  
the reaction mixture.

15 A compound of the formula (1) wherein  $R^0$  is OH can  
be converted to the corresponding compound where  $R^0$  is  
 $OR^2$  by reaction with  $R^2L$  wherein  $R^2$  is as  
hereinbefore defined and L is a leaving group such as  
20 halo e.g. bromo, chloro, iodo.

A compound of the formula (1) can be converted to a  
N-protected tetrazolyl derivative by reaction with a  
suitable N-protecting agent in standard manner, for  
25 example with a pivaloxyoxymethyl halide.

A compound of the formula (2) can suitably be  
prepared by reacting a compound of the formula (3) :



wherein Ar is as hereinbefore defined and  $L^1$  is a  
displaceable group,

35 with a compound of the formula (4) :

- 14 -



(4)

Suitably  $\text{L}^1$  in a compound of the formula (3) is hydroxy or a derivative thereof for example  $\text{L}^1$  is  
5 protected hydroxy such as silyloxy, an acid residue (for example  $\text{C}_{1-6}$ alkanoyloxy) or an ether residue (for example methoxy or ethoxy). Alternatively  $\text{L}^1$  is a secondary amino group, for example di- $\text{C}_{1-6}$ alkylamino such as dimethylamino or a cyclic amino group such as  
10 piperidino, pyrrolidino or morpholino. Preferably  $\text{L}^1$  is hydroxy or dimethylamino.

Suitably an alkali metal (e.g. sodium) salt of a compound of the formula (3) wherein  $\text{L}^1$  is hydroxy is  
15 treated with a compound of the formula (4) under mildly alkaline aqueous conditions, for example in water in the presence of piperidine and glacial acetic acid, at an elevated temperature e.g. 30 - 200°C, preferably at the reflux temperature of the reaction mixture.

20

Alternatively a compound of the formula (3) wherein  $\text{L}^1$  is a secondary amino group, for example dimethylamino, is treated with a compound of the formula  
(4) in a suitable solvent such as dimethylformamide, a  
25  $\text{C}_{1-4}$ alkanol or pyridine at an elevated temperature e.g. 30 - 200°C, preferably at the reflux temperature of the reaction mixture optionally in the presence of a base such as pyridine or an alkali metal alkoxide, e.g. sodium methoxide.

30

Compounds of the formula (3) wherein  $\text{L}^1$  is hydroxy can suitably be prepared by reaction under basic conditions of a compound of the formula (5) :

35



(5)

- 15 -

wherein Ar is as hereinbefore defined,

with a compound of the formula  $\text{HCOL}^2$  wherein  $\text{L}^2$  is a leaving group.

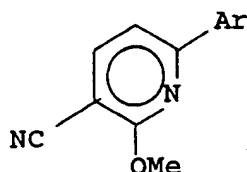
5

Suitably  $\text{L}^2$  is ethoxy or methoxy. Conveniently a solution of a compound of the formula (5) and a compound of the formula  $\text{HCOL}^2$  in a suitable organic solvent such as diethyl ether is treated with a suitable base such as an alkali metal alkoxide, e.g. sodium methoxide at ambient temperature. The resulting reaction mixture is preferably extracted with water and the aqueous extract which contains the alkali metal salt of a compound of the formula (3) wherein  $\text{L}^1$  is hydroxy is then treated with a compound of the formula (4) as hereinbefore described. Compounds of the formula (5) are known or can be prepared by methods known in the art.

Compounds of the formula (3) wherein  $\text{L}^1$  is a secondary amino group (e.g. dimethylamino) can suitably be prepared by reacting a compound of the formula (5) with a compound of the formula  $\text{HC}(\text{OR}^3)_2\text{L}^1$  wherein  $\text{R}^3$  is  $\text{C}_{1-4}$ alkyl and  $\text{L}^1$  is a secondary amino group (for example  $\text{HC}(\text{OR}^3)_2\text{L}^1$  is N,N-dimethylformamide dimethyl or diethyl acetal), or with a compound of the formula  $\text{HCL}^1_3$  where  $\text{L}^1$  is a secondary amino group (for example  $\text{HCL}^1_3$  is trisdimethylaminomethane).

Alternatively a compound of formula (2) can be prepared by demethylation of a compound of formula (6) :

- 16 -



(6)

5

10 wherein Ar is as hereinbefore defined.

Suitable demethylating agents include sodium iodide and chlorotrimethylsilane in an organic solvent such as acetonitrile, or a halohydrocarbon eg. dichloromethane or  
15 chloroform at elevated (eg. 30-80°C) or ambient temperature or sodium thiomethoxide in an organic solvent such as dimethylformamide at an elevated temperature, for example 40-120°C.

20 The Ar group in compounds of the formula (2), (5) or (6), preferably (5) or (6) may be appropriately functionalised by methods of aromatic substitution known in the art. For example, a bromo group may be introduced into a suitably substituted phenyl ring (eg. disubstituted  
25 in the 2- and 4-positions by electron-donating groups such as C<sub>1-6</sub>alkoxy) by reaction with a brominating agent such as N-bromosuccinimide or bromine in a solvent such as dimethylformamide. Alternatively a nitro group can be introduced into a phenyl ring by reaction with a suitable  
30 nitrating agent, such as nitroniumtetrafluoroborate. Such a group can be readily hydrogenated to an amino group which if desired can be converted to a NHCOR group by reaction with LCOR wherein L is a leaving group and R is as hereinbefore defined. Suitable examples of the reagent  
35 LCOR include acid halides (L is halo eg. chloro or bromo) or acid anhydrides (L is OCOR).

- 17 -

Other suitable functionalisations include the introduction of an allyl group ortho to a hydroxy substituent on a phenyl ring by reaction with an allyl halide, eg. bromide, to form an allyloxy derivative which on heating undergoes a Claisen rearrangement to form an ortho allyl hydroxy derivative. The hydroxy group can in turn be functionalised, eg. by reaction with a  $C_{1-6}$ alkyl halide to form a  $C_{1-6}$ alkoxy group. If desired, an allyl group can be converted to an E-1-propenyl group by reaction with a strong base, such as sodium methoxide. This can occur during the conversion of a compound of formula (5) to a compound of formula (2) as hereinbefore described if such a base is used. An E-1-propenyl group can be cleaved to a formyl group by reaction with an oxidising agent such as N-methylmorpholine-N-oxide in the presence of a catalyst such as osmium tetroxide to form a 1,2-dihydroxypropyl group which on reaction with an oxidising agent such as sodium periodate forms the formyl group. Alternatively the E-1-propenyl group can be converted directly to a formyl group by reaction with a mixture of osmium tetroxide and sodium periodate or by reaction with ozone. A formyl group can in turn be further functionalised, for example it can be converted to a hydroxymethyl group by reaction with a suitable reducing agent such as sodium borohydride, the hydroxymethyl group then being reacted further, eg. with a  $C_{1-6}$ alkyl halide to form a  $C_{1-6}$ alkoxymethyl group. Alternatively a formyl group can be reacted with a suitable Horner Wittig or Wittig reagent such as  $(R^4O)_2P(O)CH_2CO_2R^4$  or  $Ph_3P=CHCO_2R^4$  wherein  $R^4$  is  $C_{1-4}$ alkyl to form a  $CH=CHCO_2R^4$  group which can be optionally hydrolysed to a  $-CH=CHCO_2H$  group. A  $-CH=CHCO_2R^4$  group can be converted to a  $-CH=CHCONR_2$  group by reaction with an amine  $HNR_2$  or a chemical equivalent thereof wherein R is as hereinbefore defined. Alternatively a  $-CH=CHCO_2H$  group can be converted to an acid halide, eg. the acid chloride by reaction with oxalyl chloride, which can then

- 18 -

be reacted with an amine  $\text{HNR}_2$  or a chemical equivalent thereof. An example of a chemical equivalent is ammonium hydroxide which will form a  $\text{CH}=\text{CHCONH}_2$  group.

5           A compound of formula (6) is suitably prepared by reacting a compound of formula (2) wherein Ar is as hereinbefore defined with an O-methylating agent such as dimethylformamide dimethylacetal in dimethylformamide or trimethylphosphite at an elevated temperature (eg.  
10   40-120°C).

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the  
15   compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

20   Cyclic-AMP Protein Kinase (cA-PrK) Agonist Activity

Type II cA-PrK was prepared from the cardiac muscle of a cow. The supernatant from a muscle homogenate (3 mls of 10 mM potassium phosphate, 1 mM EDTA per g  
25   tissue) was applied to a column of DEAE-cellulose equilibrated with the homogenisation buffer and the type II cA-PrK was eluted with homogenisation buffer containing 350 mM sodium chloride (Rannels et al., 1983, Methods  
30   Enzymol., 99, 55-62).

Type II cA-PrK was assayed for phosphotransferase activity by incubating the enzyme at 30°C for 5 minutes with [  $-\text{}^{32}\text{P}$ ]-adenosine triphosphate and a suitable  
35   peptide substrate such as malantide (Malencik et al., 1983, Anal. Biochem., 132, 34-40). The reaction was

- 19 -

terminated by the addition of hydrochloric acid and the [<sup>32</sup>P]-phosphopeptide quantified by spotting the reaction mixture onto phosphocellulose papers. The concentration of compound required to give 10% phosphotransferase activation is given as the EC<sub>10</sub> (μM). The compounds of Examples 1 to 26 had EC<sub>10</sub> values in the range 10 - 130 μM.

#### Inhibition of Platelet Aggregation

Human platelet-rich-plasma was separated from freshly drawn blood (in acid/citrate/dextrose) and treated with 100 μM acetylsalicylic acid for 15 minutes at 37°C. A washed platelet suspension was then prepared in a Hepes-isotonic saline buffer after a single centrifugation step and adjusted to a concentration of 1.5x10<sup>8</sup> cells/ml. Aliquots of this suspension were pre-incubated with compounds for 5 minutes at 37°C, then challenged with 1.0 μM U46619. The extent of aggregation after 2 minutes were expressed as a percentage of control and results obtained are expressed as an IC<sub>50</sub> (concentration to cause 50% inhibition of platelet aggregation, μM). The compounds of Examples 2, 4, 5, 11-13, 15, 19-23, and 25-26 had IC<sub>50</sub> values in the range 0.8-300 μM.

#### Anti-proliferative activity

Compounds under test were dissolved in dimethylsulphoxide and diluted 1:10,000 with DMEM (Dulbecco's Modified Eagle's Medium) containing 10% fetal bovine serum to give 12.5, 25, 50 and 100 μM concentrations used in the assay. Indicator cells consisting of 3 human colorectal cells lines (SW-620, NRK-52 and HT-29) were plated at a cell density of 1000 cells in 0.1 ml of DMEM media in 96 well plates. Cells were incubated for 4 days at 37°C and 10% CO<sub>2</sub> atmosphere. On day 5, tetrazolium

- 20 -

reagent (50 µg MTT/250 µl total medium volume) was added for 16 - 20 hours. Insoluble formazan was dissolved in 150 µl of dimethylsulphoxide and absorbance was measured using a microculture plate reader at 560 nm interfaced with an IBM computer. Cell line growth and inhibition were expressed in terms of mean absorbance unit of triplicate samples following subtraction of mean background absorbance. IC<sub>50</sub> values (concentration that show 50% growth inhibition) were determined from the dose response curves. (Cancer Res., 48, 589-601, 1988). In the cell line SW-620 the compound of Example 23 had an IC<sub>50</sub> value in the range 56 - 90 µM. In the cell line NRK-52 the compound of Example 23 had an IC<sub>50</sub> value in the range 46 - 48 µM. In the cell line HT-29 the compound of Example 23 had an IC<sub>50</sub> value in the range of 55 - 66 µM.

#### Inhibition of Spontaneous Contraction in Guinea-Pig Colon

Segments of isolated guinea-pig colon (2 cm) were suspended under 2 g tension in standard organ baths containing Krebs solution. The tissues were connected at the free end to isometric transducers which allow recording and display of developed tension on chart recorders. On-line computer capture and analysis was used to quantify the effects of test compounds on spontaneous contractions. Inhibitory responses were calculated as % maximum inhibition of spontaneous contraction distance over 3 consecutive pre and post dose 2 minute readings. The concentration of compound which caused 50% inhibition of the spontaneous contraction is given as the EC<sub>50</sub> (µM). The compounds of Examples 5, 15-17 and 23 had EC<sub>50</sub> values in the range 2 - 25 µM.

- 21 -

Bronchodilatation - In vitro (Tracheal spiral)

Spiral strips of guinea-pig trachea were suspended in standard organ baths containing Krebs solution. The tissues were connected at the free end to isometric transducers which allow recording and display of developed tension on chart recorders. Tension was allowed to develop spontaneously and concentrations of test compounds added in a cumulative fashion. The concentration of compound which caused 50% inhibition of the spontaneously developed tension is given as the  $IC_{50}$  ( $\mu M$ ).

The compounds of Examples 5 and 23 had  $IC_{50}$  values of 11 and 6.5  $\mu M$  respectively.

Measurement of cardiac muscle relaxation time in rabbit ventricle

Papillary muscles from the right ventricle of female Albino New Zealand rabbits were mounted in standard organ baths containing oxygenated Krebs solution. One end of the muscle was connected to an isometric transducer which allowed recording of contractile force and its first derivative on chart recorders. Test compounds were added to the bath in a cumulative manner. Relaxation time was calculated as the time taken from peak tension to the end of the contraction. At concentrations of 30-100  $\mu M$ , compounds of Examples 12 and 23 caused a 10-20% decrease in the relaxation time indicating a lusitropic effect of use in the treatment of cardiovascular diseases such as congestive heart failure.

- 22 -

Example 1

6-(3-Methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

5

a) 3'-Methoxyacetophenone (15g) and dimethylformamide dimethylacetal (16ml) were heated together at 120°C in dimethylformamide (80ml) for 6 hours, the deep red solution was diluted with ethyl acetate (400ml), washed with water (5x100ml), dried (MgSO<sub>4</sub>) and solvent removed at reduced pressure. The oil obtained was dissolved in dimethylformamide (80ml), cyanoacetamide (10.08g) and sodium methoxide (10.8g) added and the mixture heated at 130°C for 35 minutes. The deep red solution was poured into 5% aqueous acetic acid (400ml), the precipitated product collected by filtration and washed with water, ethanol and diethyl ether. Recrystallisation from n-butanol gave 3-cyano-6-(3-methoxyphenyl)pyridin-2(1H)-one (15.14g) m.p. 251°C as a colourless solid.

20

b) 3-Cyano-6-(3-methoxyphenyl)pyridin-2(1H)-one (1g) sodium azide (0.39g) and ammonium chloride (0.32g) were heated together in N-methylpyrrolidin-2-one (10ml) at 140°C for 2 hours. The reaction mixture was poured into 10% aqueous acetic acid (150ml), the precipitated solid collected by filtration, washed with water and recrystallised from n-butanol to give the title compound (0.93g) m.p. 298°C (decomp). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 3.87(s, 3H), 6.92(d, 1H), 7.13(m, 1H), 7.41-7.50(m, 3H) and 8.48(d, 1H).

30

Example 2

6-(3-Propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

35

- 23 -

(a) 3'-Hydroxyacetophenone (13.6g), iodopropane (10.7ml) and potassium carbonate (13.8g) were heated together in dimethylformamide (80ml) at 90°C for 20hrs. The reaction mixture was diluted with ethyl acetate (400ml), washed with 2N sodium hydroxide (2x100ml) and water (4x100ml), dried (MgSO<sub>4</sub>), filtered and solvent removed at reduced pressure to give 3'-propoxyacetophenone (16.46g) as an oil. <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.99(t,3H), 1.66-1.83(m,2H), 2.58(s,3H), 3.98(t,3H), 7.19(dd,1H) and 7.39-7.57(m,3H).

10

The following compounds were similarly prepared from the appropriate phenol and alkyl iodide.

3'-Butoxyacetophenone:- oil, yield 90%, <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.94(t,3H), 1.37-1.52(m,2H), 1.66-1.77(m,2H), 2.57(s,3H), 4.02(t,2H), 7.19(dd,1H) and 7.39-7.55(m,3H).

15

3'-Benzyloxyacetophenone:- oil, yield 89%, <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 2.57(s,3H), 5.09(s,2H), 7.17(dd,1H) and 7.29-7.56(m,8H).

20

4'-Methoxy-3'-propoxyacetophenone from 3'-hydroxy-4'-methoxyacetophenone:- (A. Brossi et al J. Org. Chem., 1967, 32, 1269) :- oil, yield 71%, <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 1.05(t,3H), 1.87(m,2H), 2.56(s,3H), 3.93(s,1H), 4.04(t,2H), 6.88(d,1H), 7.52(d,1H), and 7.57(dd,1H).

25

3',5'-Dipropoxyacetophenone:- oil, yield 58%, <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.98(t,6H) 1.66-1.80(m,4H), 2.55(s,3H), 3.96(t,4H), 6.73(t,1H) and 7.04(d,2H).

30

3',5'-Diethoxyacetophenone:- oil, yield 64%, <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.42(t,6H), 2.56(s,3H), 4.05(q,4H), 6.64(t,1H) and 7.07(d,2H).

35

- 24 -

- 2',5'-Dipropoxyacetophenone:- oil, yield 64%,  $^1\text{H}$  NMR  $\delta(\text{DMSO}-d_6)$  0.96(t,3H), 1.04(t,3H), 1.62-1.84(m,4H), 2.55(s,3H), 3.88(t,2H), 3.99(t,2H) and 7.03-7.11(m,3H).
- 5 3',4'-Dipropoxyacetophenone:- yield 95%,  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.00-1.19(m,6H), 1.78-2.02(m,4H), 2.55(s,3H), 3.98-4.17(m,4H), 6.87(d,1H), 7.52(s,1H) and 7.54(d,1H).
- 10 3'-Allyloxyacetophenone:- oil, yield 71%,  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  2.58(s,3H), 4.57(d,2H), 5.27-5.47(m,2H), 5.96-6.15(m,1H), 7.12(dd,1H), 7.31(t,1H) and 7.49-7.55(m,2H).
- 15 4'-Methoxy-2'-pentyloxyacetophenone:-From 4'-methoxy-2'-hydroxyacetophenone and iodopentane, yield 92%,  $^1\text{H}$  NMR  $\delta(\text{DMSO}-d_6)$  0.86(t,3H), 1.20-1.47(m,4H), 1.74-1.85(m,2H), 2.49(s,3H), 3.82(s,3H), 4.09(t,2H), 6.56-6.62(m,2H) and 7.66(d,1H).
- 20 3'-iso-Butoxy-4'-methoxyacetophenone:-From 4'-methoxy-3'-hydroxyacetophenone and iso-butyl bromide using acetone as solvent, yield 68%.  $^1\text{H}$  NMR  $\delta(\text{DMSO}-d_6)$  0.99(d,6H), 1.96-2.15(m,1H), 2.53(s,3H), 3.78(d,1H), 3.86(s,3H), 7.06(d,1H), 7.42(d,1H) and 7.62(dd,1H).
- 25 3'-Allyloxy-4'-methoxyacetophenone:-From 4'-methoxy-3'-hydroxyacetophenone and allyl bromide, yield 67%,  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  2.55(s,3H), 3.95(s,3H), 4.63-4.68(m,2H), 5.29-5.47(m,1H), 6.02-6.18(m,1H), 6.90(d,1H), 7.53(d,1H) and 7.60(dd,1H).
- 30 3'-(2,2,-dimethylpropyloxy)-4'-methoxyacetophenone:-From 4'-methoxy-3'-hydroxyacetophenone and 1-bromo-2,2-dimethylpropane, yield 76%,  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$
- 35

- 25 -

1.07(s,9H), 2.56(s,3H), 3.69(s,2H), 6.88(d,1H) and 7.50-7.58(m,2H).

3'-ethoxy-4'-methoxyacetophenone:-from

5 3'-hydroxy-4'-methoxyacetophenone and iodoethane using acetone as solvent, yield 83%,  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.49(t,3H), 2.57(s,3H), 3.94(s,3H), 4.17(q,2H), 6.89(d,1H), 7.53-7.60(m,2H).

10 3'-Allyl-4'-methoxyacetophenone:-from

3'-allyl-4'-hydroxyacetophenone, yield 87% as an oil.  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  2.55(s,3H), 3.40(d,2H), 3.89(s,3H), 5.02-5.10(m,2H), 5.90-6.04(m,1H), 6.88(d,1H), 7.77(d,1H) and 7.85(dd,1H).

15

(b) From 3'-propoxyacetophenone (9g), 3-cyano-6-(3-propoxyphenyl)pyridin-2(1H)-one (3.49g) m.p. 240-241°C after recrystallisation from ethanol, was prepared according to the method of Example 1(a).

20

(c) From 3-cyano-6-(3-propoxyphenyl)pyridin-2(1H)-one (1g), the title compound (0.61g) m.p. 270-271°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b).

25

### Example 3

6-(3-Butoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

30

(a) 3'-Butoxyacetophenone (17.3g) and dimethylformamide dimethylacetal (11.9g) were boiled together in dimethylformamide (90ml) for 15 hours. The deep red solution was cooled to room temperature, cyanoacetamide (8.3g) and sodium methoxide (10.3g) added and the mixture 35 boiled for a further 3 hours. The reaction mixture was

- 26 -

poured into 10% aqueous acetic acid (300ml) the precipitated product separated by filtration, washed with water and recrystallised from n-butanol to give 3-cyano-6-(3-butoxyphenyl)pyridin-2(1H)-one (10.66g) m.p. 201-202°C.

(b) From 3-cyano-6-(3-butoxyphenyl)pyridin-2(1H)-one (2.15g), the title compound (0.55g) m.p. 259-260°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b).

#### Example 4

6-(3-Benzoyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 3'-benzyloxyphenylacetophenone (20.2g), 3-cyano-6-(3-benzyloxyphenyl)pyridin-2(1H)-one (2.6g) m.p. 202-203°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

(b) From 3-cyano-6-(3-benzyloxyphenyl)pyridin-2(1H)-one (1g), the title compound (0.35g) m.p. 276°C (decomp) after recrystallisation from dimethylformamide was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 5.23(s, 2H), 6.91(d, 1H), 7.16-7.20(m, 1H), 7.31-7.54(m, 8H), 8.47(d, 1H) and 12.67(br s, 1H).

#### Example 5

6-(3-Bromophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 3'-bromoacetophenone (13.2g), 3-cyano-6-(3-bromophenyl)pyridin-2(1H)-one (21.8g) m.p. 309°C (decomp) after recrystallisation from n-butanol, was prepared

- 27 -

according to the method of Example 1(a).  $^1\text{H}$  NMR  $\delta$ (DMSO- $d_6$ ) 6.89(br s, 1H), 7.48(t, 1H), 7.75(d, 1H), 7.83(d, 1H), 8.06(s, 1H), 8.21(d, 1H) and 12.75(br s, 1H).

- 5 (b) From 3-cyano-6-(3-bromophenyl)pyridin-2(1H)-one (1.37g), the title compound (0.39g) m.p. 285-286°C after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b).

10 Example 6

6-(3-Trifluoromethyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- 15 (a) From 3'-trifluoromethylacetophenone (9.4g), 3-cyano-6-(3-trifluoromethylphenyl)pyridin-2(1H)-one (11.38g) m.p. 255-256°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

- 20 (b) From 3-cyano-6-(3-trifluoromethylphenyl)pyridin-2(1H)-one (1.06g), the title compound (0.93g) m.p. 274-275°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b).

25 Example 7

6-(3-Ethylphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- 30 (a) From 3'-ethylacetophenone (7.4g), 3-cyano-6-(3-ethylphenyl)pyridin-2(1H)-one (3.97g) m.p. 241-242°C after recrystallisation from n-butanol, was prepared according to the method of Example 3(a).

- 35 (b) From 3-cyano-6-(3-ethylphenyl)pyridin-2(1H)-one (0.89g), the title compound (0.37g) m.p. 278-279°C after

- 28 -

recrystallisation from n-butanol, was prepared according to the method of Example 1(b).

#### Example 8

5

6-(4-Butoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 4'-butoxyacetophenone (5.6g), 3-cyano-6-(4-butoxyphenyl)pyridin-2(1H)-one (1.12g) m.p. 245°C after recrystallisation from ethanol, was prepared according to the method of Example 1(a).

(b) A mixture of 3-cyano-6-(4-butoxyphenyl)pyridin-2(1H)-one (0.3g), sodium azide (0.098g), ammonium chloride (0.08g) and lithium chloride (0.064g) were heated in dimethylformamide (15ml) at 120°C for 72 hours. Solvent was removed at reduced pressure, the product precipitated by the addition of 10% aqueous acetic acid (40ml) and separated by filtration. The solid was dissolved in 5% potassium hydrogen carbonate and insoluble material separated by filtration. The filtrate was acidified with conc. hydrochloric acid, the precipitated product collected by filtration and recrystallised from ethanol to give the title compound (0.05g) m.p. 289-292°C.

#### Example 9

6-(4-isoButylphenyl)pyridin-2(1H)-one

30

(a) From 4'-isobutylacetophenone (8.8g), 3-cyano-6-(4-isobutylphenyl)pyridin-2(1H)-one (6.0g) m.p. 264°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

35

- 29 -

(b) From 3-cyano-6-(4-isobutylphenyl)pyridin-2(1H)-one (2.52g), the title compound (1.54g) m.p. 275°C (decomp) after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b) but using dimethylformamide instead of N-methylpyrrolidin-2-one as solvent. <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.89(d,6H), 1.81-1.96 (m,1H), 2.51(m,2H), 6.87(d,1H), 7.33(d,2H), 7.78(d,2H), 8.46(d,1H) and 12.63(br s,1H).

10

Example 10

## 6-(4-Biphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

15 (a) From 4-acetylbiphenyl (19.6g), 6-(4-biphenyl)-3-cyanopyridin-2(1H)-one (14.01g) m.p. 312-316°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(a).

20 (b) From 6-(4-biphenyl)-3-cyanopyridin-2(1H)-one (1.36g), the title compound (0.84g) m.p. 305°C (decomp) after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 7.00(d,1H), 7.41-7.54(m,3H), 7.77(d,2H), 25 7.85(d,2H), 7.98(d,2H) and 8.50(d,1H).

Example 11

## 6-(4-Propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

30

(a) From 4'-propoxyacetophenone (15.4g) (E. Eckhart and J. Varga, Magyar. Kem. Folyoirat 1961, 67, 509, Chem Abs. 1962, 56, 15557e),  
35 3-cyano-6-(4-propoxyphenyl)pyridin-2(1H)-one (1.8g) m.p. 262-265°C after recrystallisation from dimethylformamide,

- 30 -

was prepared according to the method of Example 3(a).

(b) From 3-cyano-6-(4-propoxyphenyl)pyridin-2(1H)-one (1g), the title compound (0.85g) m.p. 292°C (decomp) after  
5 recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR  
δ(DMSO-d<sub>6</sub>) 0.99(t,3H), 1.63-1.84(m,2H), 4.02(t,2H),  
6.81(d,1H), 7.07(d,2H), 7.82(d,2H) and 8.45(d,1H).

10

#### Example 12

6-(4-Methoxy-3-propoxyphenyl)-3-(5-tetrazolyl)pyridin-  
2(1H)-one

15

(a) From 4'-methoxy-3'-propoxyacetophenone (12g), 3-cyano-  
6-(4-methoxy-3-propoxyphenyl)pyridin-2(1H)-one (14.03g)  
m.p. 241°C after recrystallisation from ethanol, was  
prepared according to the method of Example 3(a).

20

(b) From 3-cyano-6-(4-methoxy-3-propoxyphenyl)pyridin-  
2(1H)-one (3.12g), the title compound (1.69g) m.p.  
289-290°C after recrystallisation from n-butanol, was  
prepared according to the method of Example 1(b).

25

#### Example 13

6-(3,4-Methylenedioxyphenyl)-3-(5-tetrazolyl)pyridin-  
2(1H)-one

30

(a) From 3',4'-(methylenedioxy)acetophenone (16.4g),  
3-cyano-6-(3,4-methylenedioxyphenyl)pyridin-2(1H)-one  
(10.2g) m.p. >320°C after recrystallisation from dimethyl-  
formamide, was prepared according to the method of Example  
35 3(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 6.13(s,2H), 6.72(d,1H),  
7.06(d,1H), 7.36-7.42(m,2H), 8.13(d,1H) and 12.58(br s,1H).

- 31 -

(b) From 3-cyano-6-(3,4-methylenedioxyphenyl)pyridin-2(1H)-one (0.96g), the title compound (0.1g) m.p. >325°C after recrystallisation from ethanol, was prepared according to the method of Example 1(b) but using dimethylformamide instead of N-methylpyrrolidinone as solvent. <sup>1</sup>H-NMR δ(DMSO-d<sub>6</sub>) 6.14(s,2H), 6.83(d,1H), 7.08(d,1H), 7.37-7.46(m,2H), 8.43(d,1H), 12.55(br s,1H) and 13.28(br s,1H).

10

Example 14

6-(3,4-Dichlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

15 (a) From 3',4'-dichloroacetophenone (18.9g), 3-cyano-6-(3,4-dichlorophenyl)pyridin-2(1H)-one (1.94g) m.p. >330°C after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 6.97(br d,1H), 7.76-7.87 (m,2H), 8.15(s,1H) and 8.23(d,1H).

20

(b) From 3-cyano-6-(3,4-dichlorophenyl)pyridin-2(1H)-one (1.06g), the title compound (0.54g) m.p. 295°C (decomp) after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b) but using dimethylformamide instead of N-methylpyrrolidinone as solvent. <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 7.02(d,1H) 7.76-7.89 (m,2H), 8.17(s,1H) and 8.48(s,1H).

25  
30Example 15

6-(3,5-Dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

35

(a) From 3',5'-dipropoxyacetophenone (11.82g), 3-cyano-6-(3,5-dipropoxyphenyl)pyridin-2(1H)-one (7.1g) m.p.

- 32 -

209-210°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

5 (b) From 3-cyano-6-(3,5-dipropoxyphenyl)pyridin-2(1H)-one (1.25g), the title compound (1.31g) m.p. 224-225°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b).

#### Example 16

10

6-(3,5-Diethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

15 (a) From 3',5'-diethoxyacetophenone (4.16g), 3-cyano-6-(3,5-diethoxyphenyl)pyridin-2(1H)-one (1.0g) m.p. 259-261°C after recrystallisation from n-butanol, was prepared according to the method of Example 3(a).

20 (b) From 3-cyano-6-(3,5-diethoxyphenyl)pyridin-2(1H)-one (0.82g), the title compound (0.57g) m.p. 282-283°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b).

#### Example 17

25

6-(3,5-Dibromophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

30 (a) From 3',5'-dibromoacetophenone (M. Tashiro, S Mataka, H. Nakamura and K Nakayama, J. Chem. Soc. Perkin Trans I., 1988, 179) (1.11g), 3-cyano-6-(3,5-dibromophenyl)pyridin-2(1H)-one (0.73g) m.p. >300°C after recrystallisation from n-butanol, was prepared according to the method of Example 35 3(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 7.00(br d, 1H), 8.02(s, 1H), 8.09(s, 2H) and 8.23(d, 1H).

- 33 -

- (b) From 3-cyano-6-(3,5-dibromophenyl)pyridin-2(1H)-one (0.53g), the title compound (0.15g) m.p. 295-296°C (decomp) after recrystallisation from n-butanol was prepared according to the method of Example 1(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 7.10(br d, 1H), 8.02(s, 1H), 8.13(s, 2H) and 8.47(d, 1H).

Example 18

- 10 6-(2,4-Dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one
- (a) From 2',4'-dipropoxyacetophenone (17.9g) (P. Chabrier, H. Najer, R. Giudicelli and E. Joannie-Voisinet, Bull. Soc. Chim. France, 1958, 1488.), 3-cyano-6-(2,4-dipropoxyphenyl)pyridin-2(1H)-one (1.69g) m.p. 148°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).
- 20 (b) From 3-cyano-6-(2,4-dipropoxyphenyl)pyridin-2(1H)-one (1g), the title compound (0.60g) m.p. 205°C after recrystallisation twice from ethanol, was prepared according to the method of Example 1(b).

Example 19

- 25 6-(2,5-Dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one
- 30 (a) From 2',5'-dipropoxyphenylacetophenone (11.8g), 3-cyano-6-(2,5-dipropoxyphenyl)pyridin-2(1H)-one (14.36g) m.p. 160-162°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.92(t, 3H), 0.97(t, 3H), 1.61-1.76(m, 4H), 3.92(t, 4H), 6.54(d, 1H), 7.01-7.06(m, 3H), 8.18(d, 1H).
- 35

- 34 -

(b) From 3-cyano-6-(2,5-dipropoxyphenyl)pyridin-2(1H)-one (2.5g), the title compound (0.81g) m.p.188-189°C after recrystallisation from ethanol, was prepared according to the method of Example 1(b).

5

Example 20

6-(2,3,4-Trichlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

10

(a) 2',3',4'-Trichloroacetophenone (22.15g) and dimethylformamide (12.5g) were boiled in dimethylformamide (100ml) for 3 hours. The solution was diluted with ethyl acetate (500ml), washed with water (6x100ml), dried (MgSO<sub>4</sub>), filtered and solvent removed at reduced pressure. The residue was triturated with diethyl ether to give 3-N,N-dimethylamino-1-(2,3,4-trichlorophenyl)prop-2-ene-1-one (17.5g). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 2.84(s,3H), 3.08(br s,3H), 5.17(d,1H), 7.1(very br,1H), 7.30(br d,1H) and 7.65(d,1H).

20

(b) A solution of 3-N,N-dimethylamino-1-(2,3,4-trichlorophenyl)prop-2-ene-1-one (9.8g) and cyanoacetamide (3.18g) in dimethylformamide (35ml) was boiled for 48 hours. The reaction mixture was poured into 10% aqueous acetic acid (100ml), the precipitated product separated by filtration and recrystallised from ethanol to give 3-cyano-6-(2,3,4-trichlorophenyl)pyridin-2(1H)-one (4.4g). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 6.52(d,1H), 7.58(d,1H), 7.79(d,1H), 8.24(d,1H) and 12.95(br s,1H).

30

(c) From 3-cyano-6-(2,3,4-trichlorophenyl)pyridin-2(1H)-one (1.2g), the title compound (1.21g) m.p.>300°C after recrystallisation from dimethylformamide/water, was prepared according to the method of Example 1(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 6.63(d,1H), 7.61(d,1H), 7.83(d,1H),

35

- 35 -

8.51(d, 1H) and 12.98(br s, 1H).

Example 21

5 6-[6-(1,2,3,4-Tetrahydronaphthyl)]-3-(5-tetrazolyl)pyridin-  
2(1H)-one

- (a) From 6-acetyltetralin (4.23g), 3-cyano-6-[6-(1,2,3,4-tetrahydronaphthyl)]pyridin-2(1H)-one (1.27g) m.p. 245-246°C after recrystallisation from n-butanol, was prepared according to the method of Example 3(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.75(m, 4H), 2.77(m, 4H), 6.71(d, 1H), 7.19(d, 1H), 7.50(d, 1H), 7.53(s, 1H) and 8.15(d, 1H).
- 10
- (b) From 3-cyano-6-[6-(1,2,3,4-tetrahydronaphthyl)]pyridin-2(1H)-one (1g), the title compound (0.55g) m.p. 284-285°C after recrystallisation from dimethylformamide/water, was prepared according to the method of Example 1(b).
- 15

20

Example 22

6-(3-Chlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- 25 (a) From 3'-chloroacetophenone (15.46g), 6-(3-chlorophenyl)-3-cyanopyridin-2(1H)-one (17.12g) m.p. 304-305°C after recrystallisation from n-butanol, was prepared according to the method of Example 3(a).
- (b) From 6-(3-chlorophenyl)pyridin-2(1H)-one (1.2g), the title compound (1.01g) m.p. 301-302°C (decomp) after recrystallisation from n-butanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 6.94(d, 1H), 7.48-7.62(m, 2H), 7.81(d, 1H), 7.96(s, 1H),
- 30
- 35 8.48(d, 1H) and 12.77(br s, 1H)

- 36 -

Example 23

6-(3-Phenylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

5

(a) 3'-Phenylthioacetophenone (2.05g) (L. Victor, Brit. Pat. 1,519,354) and dimethylformamide dimethylacetal (1.19g) were heated together in dimethylformamide (10ml) at 100°C for 18 hours. The reaction mixture was diluted  
10 with ethyl acetate (50ml) washed with water (6x30ml), dried (MgSO<sub>4</sub>) filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane-5% ethanol/dichloromethane eluant) to give 3-N,N-dimethylamino-1-(3-phenylthiophenyl)-  
15 prop-2-ene-1-one (1.72g) as a yellow oil.

(b) A mixture of 3-N,N-dimethylamino-1-(3-phenylthiophenyl)prop-2-ene-1-one (1.72g), sodium methoxide (0.76g) and cyanoacetamide (0.59g) were boiled together in  
20 dimethylformamide (10ml) for 1 hour. The reaction mixture was poured into 10% aqueous acetic acid (100ml), the precipitated product separated by filtration and recrystallised from ethanol to give 3-cyano-6-(3-  
25 phenylthiophenyl)pyridin-2(1H)-one (1.0g) m.p. 262-264°C.

(c) From 3-cyano-6-(3-phenylthiophenyl)pyridin-2(1H)-one (0.79g), the title compound (0.77g) m.p. 265-266°C after  
recrystallisation from n-butanol, was prepared according  
30 to the method of Example 1(b).

Example 24

35 3,4-Dimethoxyphenyl-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 3',4'-Dimethoxyacetophenone (18g), 3-cyano-6-

- 37 -

(3,4-dimethoxyphenyl)pyridin-2(1H)-one (9.86g) m.p. 269-270°C after recrystallisation from ethanol, was prepared according to the method of Example 1(a).

- 5 (b) From 3-cyano-6-(3,4-dimethoxyphenyl)pyridin-2(1H)-one (1.02g), the title compound (0.02g) m.p. 293-295°C after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b).

10 Example 25

6-(3-Methylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- 15 (a) From 3'-methylthioacetophenone (4.64g), 3-cyano-6-(3-methylthiophenyl)pyridin-2(1H)-one (4.3g) m.p. 234-238°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

- 20 (b) From 3-cyano-6-(3-methylthiophenyl)pyridin-2(1H)-one (1g), the title compound (0.85g) m.p. 274-276°C (decomp) after recrystallisation from n-butanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR  
25  $\delta$ (DMSO-d<sub>6</sub>) 2.58(s,3H), 6.91(d,1H), 7.39-7.63(m,3H),  
7.68(s,1H) and 8.47(d,1H).

Example 26

6-(3-Butylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

30

- (a) Copper-(I)-n-butylmercaptide (R. Adams, W. Reijsschneider and A. Ferretti, Org, Syn. Coll. Vol., V, p107) (3.34g) and 3-cyano-6-(3-bromophenyl)pyridin-  
35 2(1H)-one (2.61g) were heated together in a mixture of quinoline (10ml) and pyridine (3ml) at 160°C for 4 hours.

- 38 -

The reaction mixture was poured onto conc. hydrochloric acid (30ml) and ice (100g) and the precipitated material collected by filtration. The residue was column chromatographed (silica gel, dichloromethane-dichloromethane/2% ethanol) to give 3-cyano-6-(3-butylthiophenyl)pyridin-2(1H)-one (0.35g) m.p. 191-193°C after recrystallisation from ethanol.

(b) From 3-cyano-6-(3-butylthiophenyl)pyridin-2(1H)-one (0.23g), the title compound (0.11g) m.p. 237-238°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b).

#### Example 27

6-(3,4-Di-Propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 3',4'-di-propoxyacetophenone (3.6g) 3-cyano-6-(3,4-dipropoxyphenyl)pyridin-2(1H)-one (3.21g) m.p. 249°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

(b) From 3-cyano-6-(3,4-di-propoxyphenyl)-pyridin-2(1H)-one (1.00g) the title compound m.p. 280°C (decomp) after recrystallisation from n-butanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR (δ<sub>DMSO</sub>) 0.97-1.05(m, 6H), 1.71-1.81(m, 4H), 4.01(t, 2H), 4.03(t, 2H), 6.88(d, 1H), 7.09(d, 1H), 7.43(d, 1H), 7.46(s, 1H) and 8.44(d, 1H) and 12.61(br.s, 1H).

#### Example 28

6-(2,3-di-Propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- 39 -

(a) From 2,3-dihydroxybenzaldehyde (20g), 2,3-di-propoxybenzaldehyde (18.6g) isolated as an oil was prepared according to the method of Example 2(a).  $^1\text{H-NMR}$   $\delta(\text{CDCl}_3)$  1.04(t,3H), 1.09(t,3H), 1.74-1.96(m,4H),  
5 3.97(t,2H), 4.15(t,3H), 7.03-7.16(m,2H), 7.39(dd,1H) and 10.47(s,1H)

(b) To a solution of 2,3-di-propoxybenzaldehyde (18.6g) in tetrahydrofuran at  $-78^\circ\text{C}$  methyl lithium (61ml, 1.5M in  
10 diethyl ether) was added over 10 minutes. The reaction mixture was stirred at  $-78^\circ\text{C}$  for two hours and at room temperature for 16 hours. After quenching with water the organic phase was separated, dried ( $\text{MgSO}_4$ ) and solvent removed to give 1-(2,3-di-propoxyphenyl)-1-hydroxyethane  
15 (20g) as an oil.  $^1\text{H-NMR}$   $\delta(\text{CDCl}_3)$  1.04(t,3H), 1.06(t,3H), 1.72-1.93(m,4H), 3.89(t,2H), 3.99(t,2H), 5.15(m,1H), 6.80(m,1H) and 6.95-7.04(m,2H).

(c) To an ice cooled solution of 1-(2,3-di-propoxyphenyl)-1-hydroxyethane (20g) in dichloromethane (250ml)  
20 powdered 4Å molecular sieves (23g), N-methylmorpholine-N-oxide (14.9g) and tetrapropylammonium perruthenate (1g). The mixture was stirred for one hour with ice cooling and at room temperature overnight. After filtration through  
25 Hyflo solvent was removed at reduced pressure to give 2',3'-di-propoxyacetophenone (18.3g).  $^1\text{H-NMR}$   $\delta(\text{CDCl}_3)$  1.03(t,3H), 1.08(t,3H), 1.72-1.96(m,4H), 2.63(s,3H), 3.96(t,2H), 4.01(t,2H) and 6.99-7.19(m,3H).

30 (d) From 2',3'-dipropoxyacetophenone (10g), 3-cyano-6-(2,3-di-propoxyphenyl)pyridin-2(1H)-one (1.87g) m.p.  $195-198^\circ\text{C}$  was prepared according to the method of Example 3(a), omitting sodium methoxide.  $^1\text{H-NMR}$  ( $d_6$ -DMSO) 0.81(t,3H), 1.01(t,3H), 1.51(m,2H),  
35 1.76(m,2H), 3.84(t,2H), 3.99(t,2H), 6.43(d,1H), 6.97(d,1H), 7.10- 7.27(m,2H) and 8.17(d,1H).

- 40 -

(e) From 3-cyano-6-(2,3-di-propoxyphenyl)pyridin-2(1H)-one (1g), the title compound (0.47g) m.p. 186-187°C after recrystallisation from aqueous ethanol was prepared according to the method of Example 1(b).

5

Example 29

6-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one

10

(a) A mixture of 3'-hydroxy-4'-methoxyacetophenone (20.8g), potassium carbonate (24.15g), cyclopentyl bromide (22.35g) and potassium iodide (3.32g) were combined in acetone (250ml) and boiled for 24 hours. Dimethylformamide (25ml) was added and boiling continued for a further 24 hours. The reaction mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was dissolved in diethyl ether (200ml) washed with 2N sodium hydroxide (3x50ml) and water, dried and solvent removed at reduced pressure to give 3'-cyclopentyloxy, 4'-methoxyacetophenone as an oil that solidified on standing m.p. 59-60°C.

15

(b) From 3'-cyclopentyloxy-4'-methoxyacetophenone (11.25g), 3-cyano-6-(3-cyclopentyloxy-4-methoxyphenyl)-pyridin-2(1H)-one (4.07g) m.p. 259-260°C after digestion with acetonitrile was prepared according to the method of Example 3(a) omitting sodium methoxide.

25

(c) From 3-cyano-6-(3-cyclopentyloxyphenyl-4-methoxyphenyl)pyridin-2(1H)-one (0.8g), the title compound (0.6g) m.p. 286-287°C (decomp) after recrystallisation from dimethylformamide was prepared according to the method of Example 1(b). <sup>1</sup>H-NMR δ(d<sub>6</sub>-DMSO)

30

- 41 -

1.54-2.02(m,8H), 3.83(s,3H), 5.00(m,1H), 6.87(d,1H),  
7.10(d,1H), 7.43(s,1H), 7.46(d,1H) and 8.44(d,1H).

Example 30

5

6-(3-Ethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

10 (a) A mixture of 3-hydroxyacetophenone (6.8g) and  
tris(dimethylamino)methane (14.5g) were heated together in  
dimethylformamide (30ml) at 80°C for 4 hours. The reaction  
mixture was cooled to room temperature cyanoacetamide  
(8.4g) added and the mixture boiled for 8 hours. After  
15 cooling to room temperature the mixture was poured into  
10% aqueous acetic acid (200ml), filtered and the residue  
washed with water and ethanol to give 3-cyano-6-(3-  
hydroxyphenyl)pyridin-2(1H)-one. <sup>1</sup>H-NMR δ(d<sub>6</sub>-DMSO)  
6.64(br.d,1H), 6.95(dd,1H), 7.12(s,1H), 7.20(d,1H),  
7.32(t,1H), 8.15(d,1H), 9.87(s,1H) and 12.70(br.s,1H).

20

(b) To a suspension of sodium hydride (1g, 50% in oil) in  
dimethylformamide (15ml) 3-cyano-6-(3-hydroxy-  
phenyl)pyridin-2(1H)-one (2.12g) was added in portions  
over 30 minutes. When gas evolution had ceased  
25 iodoethane (1.56g) was added and the mixture stirred  
overnight. The mixture was diluted with ethyl acetate  
(100ml), washed with 2N hydrochloric acid (2x30ml) and  
with water (4x50ml), dried (MgSO<sub>4</sub>) and solvent removed  
at reduced pressure. The residue was recrystallised from  
30 n-butanol to give 3-cyano-6-(3-ethoxyphenyl)pyridin-  
2(1H)-one (0.68g). <sup>1</sup>H-NMR δ(d<sub>6</sub>-DMSO) 1.35(t,3H),  
4.12(q,2H), 6.80(d,1H), 7.08(d,1H), 7.31-7.47(m,3H) and  
8.18(d,1H).

35

(c) From 3-cyano-6-(3-ethoxyphenyl)pyridin-2(1H)-one  
(0.5g), the title compound (0.44g) m.p.279°C (decomp)

- 42 -

after recrystallisation from n-butanol, was prepared according to the method of Example 1(b).  $^1\text{H}$ -NMR  $\delta$ ( $\text{d}_6$ -DMSO) 1.36(t,3H), 4.14(q,2H), 6.90(d,1H), 7.10(m,1H), 7.34-7.48(m,3H) and 8.47(d,1H).

5

Example 31

6-(3,5-Dimethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

10

(a) From 3',5'-dimethoxyacetophenone (4.1g), 3-cyano-6-(3,5-dimethoxyphenyl)pyridin-2(1H)-one (2.41g) m.p. 297°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

15

(b) From 3-cyano-6-(3,5-dimethoxyphenyl)pyridin-2(1H)-one (1.4g), the title compound (1.36g) m.p. 338°C (decomp) after recrystallisation from acetonitrile/dimethylformamide was prepared according to the method of Example 1(b).  $^1\text{H}$  NMR  $\delta$ ( $\text{d}_6$ -DMSO) 3.86(s,6H), 6.66(m,1H), 6.95(d,1H), 7.02(m,2H), 8.47(d,1H) and 12.66(br.s,1H).

20

Example 32

25 6-(2-Butylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 2'-bromoacetophenone (19.9g), 6-(2-bromophenyl)-3-cyanopyridin-2(1H)-one (11.4g) m.p. 245-246°C after recrystallisation from ethanol, was prepared according to the method of Example 1(a).

30

(b) From 6-(2-bromophenyl)-3-cyanopyridin-2(1H)-one (2.61g), 6-(2-butylthiophenyl)-3-cyanopyridin-2(1H)-one (0.83g) m.p. 163-165°C after recrystallisation from

35

- 43 -

ethanol, was prepared according to the method of Example 26(a).

- 5 (c) From 6-(2-butylthiophenyl)-3-cyanopyridin-2(1H)-one (0.71g), the title compound (0.53g) m.p.181-182°C after recrystallisation from ethanol, was prepared according to the method of Example 1(b).

### Example 33

- 10 6-(3-Allyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- 15 (a) From 3'-allyloxyacetophenone (15.07g), 6-(3-allyloxyphenyl)-3-cyanopyridin-2(1H)-one (14.7g) was prepared according to the method of Example 3(a). <sup>1</sup>H NMR δ(d<sub>6</sub>-DMSO) 4.67(d,2H), 5.26-5.46(m,2H), 5.98-6.20(m,1H), 6.80(d,1H), 7.13(m,1H), 7.33(m,3H) and 8.20(d,1H).

- 20 (b) From 6-(3-allyloxyphenyl)-3-cyanopyridin-2(1H)-one (1g), the title compound (0.34g) m.p.260°C (decomp) after recrystallisation from n-butanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(d<sub>6</sub>-DMSO)  
25 4.72(m,2H), 5.28-5.52(m,2H), 6.04-6.20(m,1H), 6.94(d,1H), 7.14(m,1H), 7.48(m,3H) and 8.47(d,1H).

### Example 34

- 30 6-(4-Methoxy-2-pentyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- (a) From 4'-methoxy-2'-pentyloxyacetophenone (11.8g), 3-cyano-6-(4-methoxy-2-pentyloxyphenyl)pyridin-2(1H)-one (3.4g) m.p. 143-144°C after recrystallisation from ethanol,  
35 was prepared according to the method of Example 3(a).

- 44 -

(b) From 3-cyano-6-(4-methoxy-2-pentyloxyphenyl)pyridin-2(1H)-one (1.25g), the title compound (0.65g) m.p. 193-194°C after recrystallisation from ethanol was prepared according to the method of Example 1(b).

5

### Example 35

6-(3-iso-Butoxy-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

10

(a) From 3'-iso-butoxy-4'-methoxyacetophenone (7.6g), 3-cyano-6-(3-iso-butoxy-4-methoxyphenyl)pyridin-2(1H)-one (6.02g) m.p. 234-235°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

15

(b) From 3-cyano-6-(3-iso-butoxy-4-methoxyphenyl)pyridin-2(1H)-one (1.19g), the title compound (1.2g) m.p. 296-297°C (decomp) after recrystallisation from ethanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>)

20 1.01(d, 6H), 2.02-2.16(m, 1H), 3.85(s, 3H), 3.89(d, 2H), 6.89(d, 1H), 7.12(d, 1H), 7.41-7.50(m, 2H) and 8.47(d, 1H).

### Example 36

25 6-(2-Bromo-3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) To an ice cooled solution of 3',5'-diethoxyacetophenone (10.4g) in dimethylformamide (50ml) N-bromosuccinimide (9.79g) was added in portions over 1 hour. The mixture was stirred at 0°C for 3 hours and stood at room temperature for 48 hours. After diluting with ethyl acetate (200ml) the mixture was washed with water (5x100ml), dried (MgSO<sub>4</sub>) and solvent removed at reduced pressure to give 2'-bromo-3',5'-diethoxyacetophenone (12.53g) as an oil. <sup>1</sup>H NMR δ(CDCl<sub>3</sub>)

30 1.41(t, 3H), 1.50(t, 3H), 2.60(s, 3H), 4.00(q, 2H), 4.10(q, 2H), 6.45(d, 1H) and 6.50(d, 1H).

35

- 45 -

(b) From 2'-bromo-3',5'-diethoxyacetophenone (4.31g), 3-cyano-6-(2-bromo-3,5-diethoxyphenyl)pyridin-2(1H)-one (0.75g) m.p. 234-235°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

(c) From 3-cyano-6-(2-bromo-3,5-diethoxyphenyl)pyridin-2(1H)-one (0.6g), the title compound m.p. 276°C after recrystallisation from ethanol was prepared according to the method of Example 1(b).

### Example 37

15 6-(5-Bromo-4-methoxy-2-pentyloxyphenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one

(a) A mixture of 3-cyano-6-(4-methoxy-2-pentyloxyphenyl)-pyridin-2(1H)-one (1.71g), silver carbonate (1.92g) and iodomethane in chloroform (30ml) were stirred in the dark for 48 hours. After filtration (celite pad) solvent was removed at reduced pressure and the residue column chromatographed (silica gel, 40%hexane/dichloromethane eluant) to give 3-cyano-2-methoxy-6-(4-methoxy-2-pentyloxyphenyl)pyridine (1.45g) m.p. 76-78°C.

(b) To a cooled (ice bath) solution of 3-cyano-2-methoxy-6-(4-methoxy-2-pentyloxyphenyl)pyridine (1.3g) in dimethylformamide (10ml) N-bromosuccinimide (0.71g) was added in portions over 30 minutes. The solution was stirred at room temperature overnight diluted with ethyl acetate (50ml) and washed with water (5x50ml). The organic phase was dried (MgSO<sub>4</sub>) solvent removed at reduced pressure and the residue recrystallised from ethanol to give 3-cyano-2-methoxy-6-(5-bromo-4-methoxy-2-pentyloxyphenyl)pyridine (1.1g) m.p. 136-137°C.

- 46 -

(c) 3-Cyano-2-methoxy-6-(2-bromo-4-methoxy-2-pentyloxyphenyl)pyridine (1g) and sodium iodide (1.50g) (dried at 70°C in vacuo for 4 hours) were dissolved in acetonitrile (10ml) and chlorotrimethylsilane (1.08g) added. The reaction mixture was stirred in the dark for 2 hours, diluted with ethyl acetate (50ml) washed with water (2x50ml), with 5% aqueous sodium metabisulphite (30ml) and water (50ml). The organic phase was dried (MgSO<sub>4</sub>) solvent removed at reduced pressure and the residue recrystallised from ethanol to give 3-cyano-6-(5-bromo-4-methoxy-2-pentyloxyphenyl)pyridin-2(1H)-one (0.55g) m.p.188-190°C.

(d) From 3-cyano-6-(5-bromo-4-methoxy-2-pentyloxyphenyl)pyridin-2(1H)-one (0.5g), the title compound (0.38g) m.p.246-248°C after recrystallisation from ethanol, was prepared according to the method of Example 1(b).

### Example 38

6-(2-Allyl-4-methoxy-3-propoxyphenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one

(a) A mixture of 3'-allyloxy-4'-methoxyacetophenone (7.76g) and diethylaniline (5.96g) was degassed with nitrogen for 15 minutes and heated at 215°C for 90 minutes. After cooling to room temperature the reaction mixture was dissolved in ethyl acetate (100ml) and washed with 2N hydrochloric acid (3x100ml). The organic phase was dried (MgSO<sub>4</sub>) and solvent removed at reduced pressure to give after recrystallisation from ethanol/water 2'-allyl-3'-hydroxy-4'-methoxyacetophenone (5.1g) m.p.81-83°C.

(b) 2'-Allyl-3'-hydroxy-4'-methoxyacetophenone (5.0g), potassium carbonate (3.3g) and iodopropane were heated together in a mixture of dimethylformamide (20ml) and butanone (30ml) for 48 hours. The mixture was filtered and

- 47 -

- solvent removed from the filtrate at reduced pressure to give a residue which was dissolved in ethyl acetate (100ml) and washed with water (5x50ml). The organic phase was dried (MgSO<sub>4</sub>) and solvent removed at reduced pressure to give 2'-allyl-4'-methoxy-3'-propoxyacetophenone (5.0g) as an oil.
- 5 <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.98(t, 3H), 1.62-1.80(m, 2H), 2.48(s, 3H), 3.62-3.69(m, 2H), 3.79(t, 2H), 3.85(s, 3H), 4.82-4.91(m, 2H), 5.78-5.93(m, 1H), 6.99(d, 1H) and 7.63(d, 1H).
- 10 (c) From 2'-allyl-4'-methoxy-3'-propoxyacetophenone (4.96g) 3-cyano-6-(2-allyl-4-methoxy-3-propoxyphenyl)pyridin-2(1H)-one (1.15g) m.p. 170-171°C after recrystallisation from ethanol was prepared according to the method of Example 3(a) with, however, the omission of sodium methoxide.
- 15 (d) From 3-cyano-6-(2-allyl-4-methoxy-3-propoxyphenyl)pyridin-2(1H)-one (0.49g), the title compound (0.24g) m.p. 210-211°C after recrystallisation from ethanol was prepared according to the method of Example 1(b).

20

Example 39

6-[3-(E-1-propenyl)-4-methoxyphenyl]-3-(5-tetrazolyl)-pyridin-2(1H)-one

25

- (a) From 3-allyl-4-methoxyacetophenone (7.6g), 3-cyano-6-[3-(E-1-propenyl)-4-methoxyphenyl]pyridin-2(1H)-one (4g) after recrystallisation from n-butanol, was prepared according to the method of Example 3(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>)
- 30 1.88(d, 3H), 3.87(s, 3H), 6.40-6.67(m, 3H), 6.78(d, 1H), 7.10(d, 1H), 7.72(dd, 1H), 7.93(d, 1H) and 8.14(d, 1H).

- (b) From 3-cyano-6-[3-(E-1-propenyl)-4-methoxyphenyl]pyridin-2(1H)-one (2.13g), the title compound
- 35 (0.8g) m.p. 291-295°C (decomp) after recrystallisation from dimethylformamide was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.89(d, 3H), 3.88(s, 3H),

- 48 -

6.42-6.71(m, 3H), 6.90(d, 1H), 7.12(d, 1H), 7.76(dd, 1H),  
7.97(d, 1H) and 8.44(d, 1H).

#### Example 40

5

6-(4-Methoxy-3-propoxyphenyl)-3-[5-(1-pivaloyloxymethyl)-  
tetrazolyl]pyridin-2(1H)-one and 6-(4-methoxy-3-  
propoxyphenyl)-3-[5-(2-pivaloyloxymethyl)-  
tetrazolyl]pyridin-2(1H)-one

10

A mixture of 4-methoxy-3-propoxyphenyl)-3-(5-  
tetrazolyl]pyridin-2(1H)-one (1.64g), pivaloyloxymethyl  
chloride (0.75g), sodium hydrogen carbonate (420mg) and  
sodium iodide (50mg) were heated in dimethylformamide (5ml)  
15 at 70°C for 24 hours. The mixture was diluted with ethyl  
acetate (50ml) and washed with water 6 x 50ml). The organic  
phase was dried (MgSO<sub>4</sub>) filtered and solvent removed at  
reduced pressure. The residue was column chromatographed  
(silica gel, 70% hexane/ethyl acetate - 30% hexane/ethyl  
20 acetate eluant to give:- a) 6-(4-methoxy-3-propoxyphenyl)-  
3-[5-(1-pivaloyloxymethyl)tetrazolyl]pyridin-2(1H)-one  
(0.26g) m.p. 169-170°C after recrystallisation from ethanol  
and b) 6-(4-methoxy-3-propoxyphenyl)-3-[5-(2-  
pivaloyloxymethyl)tetrazolyl]pyridin-2(1H)-one (0.35g)  
25 m.p.195-196°C after recrystallisation from ethanol.

#### Example 41

6-[3-Ethoxy-5-(2-methoxyethoxy)phenyl]-3-(5-tetrazolyl)-  
30 pyridin-2(1H)-one

a) 3',5'-Dihydroxyacetophenone (15.2g), potassium carbonate  
(7.59g) and iodoethane (17.16g) were combined and heated at  
reflux for 15 hours. Additional potassium carbonate (2.76g)  
35 and iodoethane (6.2g) were added and heating was continued  
for a further 10 hours. The reaction mixture was filtered,  
solvent removed at reduced pressure, the residue dissolved

- 49 -

- in ethyl acetate (100ml) and extracted with 2N sodium hydroxide (3x50ml). The combined basic extracts were washed with ethyl acetate (2x50ml), acidified with 2N hydrochloric acid and extracted with dichloromethane (3x100ml). The combined dichloromethane extracts were washed with water (2x50ml), dried (MgSO<sub>4</sub>), filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane eluant) to give 3'-ethoxy-5'-hydroxyacetophenone (4.83g) m.p. 96-98°C.
- 10 b) To a suspension of sodium hydride (0.92g, 60% in oil washed with hexane) in dimethylformamide (10ml), 3'-ethoxy-5'-hydroxyacetophenone (3.24g) was added in portions over 10 minutes. When gas evolution had ceased chloroethylmethyl ether (1.9g) and sodium iodide (50mg) were added and the mixture heated to 90°C for 18 hours and stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate (100ml), washed with 2N sodium hydroxide (3x50ml) and water (3x50ml). The organic phase was dried (MgSO<sub>4</sub>), filtered and solvent removed at reduced pressure to give 3'-ethoxy-5'-(2-methoxyethoxy)acetophenone (4.03g) as an oil. <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 1.42(t,3H), 2.56(s,3H), 3.46(s,3H), 3.74-3.78(m,2H), 4.05(q,2H), 4.13-4.17(m,2H), 6.68(m,1H) and 7.10(m,2H).
- 25 c) From 3'-ethoxy-5'-(2-methoxyethoxy)acetophenone, 3-cyano-6-[3-ethoxy-5-(2-methoxyethoxy)phenyl]pyridin-2(1H)-one (1.1g) m.p.199°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).
- 30 d) From 3-cyano-6-[3-ethoxy-5-(2-methoxyethoxy)phenyl]pyridin-2(1H)-one (0.94g), the title compound (0.6g) m.p.205-206°C after recrystallisation from ethanol, was prepared according to the method of Example 35 1(b).

Example 42**6-(3-(2,2-Dimethylpropyloxy)-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one**

5

a) From 3'-(2,2-dimethylpropyloxy)-4'-methoxyacetophenone (9.0g), 3-cyano-6-[3-(2,2-dimethylpropyloxy)-4-methoxyphenyl]pyridin-2(1H)-one (3.46g) was prepared according to the method of Example 3(a). <sup>1</sup>H NMR δ(DMSO d<sub>6</sub>) 1.02(s,9H), 3.74(s,2H), 3.85(s,3H), 6.79(d,1H), 7.09(d,1H), 7.42(s,1H), 7.43(d,1H) and 8.14(d,1H).

10

b) From 3-cyano-6-[3-(2,2-dimethylpropyloxy)-4-methoxyphenyl]pyridin-2(1H)-one (1.25g), the title compound (1.28g) m.p. >300°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.04(s,9H), 3.77(s,2H), 3.86(s,3H), 6.90(d,1H), 7.10(d,1H), 7.45(m,2H) and 8.44(d,1H).

15

Example 43**6-(3-Ethoxy-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one**

a) From 3'-ethoxy-4'-methoxyacetophenone (2.91g), 3-cyano-6-(3-ethoxy-4-methoxyphenyl)pyridin-2(1H)-one (2.02g) m.p.273°C after recrystallisation from ethanol was prepared according to the method of Example 1(a).

25

b) From 3-cyano-6-(3-ethoxy-4-methoxyphenyl)pyridin-2(1H)-one (1.0g), the title compound (1.06g) m.p.299°C (decomp) after recrystallisation from n-butanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.37(t,3H), 3.84(s,3H), 4.15(q,2H), 6.92(d,1H), 7.10(d,1H), 7.41-7.50(m,2H) and 8.43(d,1H).

30

35

- 51 -

Example 44**6-(3-Propionamidophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one**

- 5 a) To a stirred suspension of sodium methoxide (4.32g) in diethyl ether (50ml) a mixture of 3'-propionamidoacetophenone (5.73g) and ethyl formate (4.44g) in tetrahydrofuran (100ml) was added over 30 minutes. After stirring overnight the mixture was filtered and the residue  
10 washed with diethyl ether. The residue was dissolved in water (50ml), the pH adjusted to 9.0 with glacial acetic acid and cyanoacetamide (4.2g) added. The solution obtained was boiled overnight cooled to room temperature and adjusted to pH 5 with glacial acetic acid (US Patent  
15 4,278,681). The precipitated material was collected by filtration, washed thoroughly (4x50ml) with ethanol and recrystallised from dimethylformamide/water to give 3-cyano-6-(3-propionamidophenyl)pyridin-2(1H)-one (0.4g) m.p. 328-330°C  
20
- b) From 3-cyano-6-(3-propionamidophenyl)pyridin-2(1H)-one (0.3g) the title compound (0.2g) m.p.291-293°C (decomp) after recrystallisation from dimethylformamide/water, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR  
25 δ(DMSO-d<sub>6</sub>) 1.11(t,3H), 2.37(q,2H), 6.75(d,1H), 7.46(m,2H), 7.69(m,1H), 8.09(m,1H) and 8.50(d,1H).

Example 45

30 **6-(4-Methoxy-3-propylphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one (SB 20525)**

- (a) A solution of 3'-allyl-4'-methoxyacetophenone (20g) in ethanol (250ml) containing 10% palladium on charcoal (2g)  
35 was treated with hydrogen at 50 p.s.i until the calculated volume of hydrogen had been taken up. The mixture was filtered (celite pad) and solvent removed at reduced

- 52 -

- pressure. The residue was dissolved in dichloromethane (100ml) and manganese dioxide (60g) added. The mixture was stirred at room temperature for 48 hours, filtered (celite pad) and solvent removed at reduced pressure to give 4'-methoxy-3'-propylacetophenone (15.16g) as an oil. <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 0.95(t, 3H), 1.52-1.79(m, 2H), 2.55(s, 3H), 2.61(t, 2H), 3.88(s, 3H), 6.86(d, 1H), 7.77(d, 1H) and 7.82(dd, 1H).
- 10 (b) From 4'-methoxy-3'-propylacetophenone (5.77g), 3-cyano-6-(4-methoxy-3-propylphenyl)pyridin-2(1H)-one (4.43g) m.p. 239°C after recrystallisation from butanol, was prepared according to the method of Example 3(a).
- 15 (c) From 3-cyano-6-(4-methoxy-3-propylphenyl)pyridin-2(1H)-one (4.02g), the title compound (3.64g) m.p. 293-294°C (decomp) after recrystallisation from ethanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.93(t, 3H), 1.51-1.71(m, 2H), 2.59(t, 2H), 3.87(s, 3H), 20 6.83(d, 1H), 7.10(d, 1H), 7.68-7.74(m, 2H) and 8.46(d, 1H).

#### Example 46

- 25 6-(3-Bromo-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one (SB 204617)

- (a) From 3'-bromo-4'-methoxyacetophenone (K.W.Rosenmund et. al. Chem. Ber., 1922, 90, 1957) (2.29g), 3-cyano-6-(3-bromo-4-methoxyphenyl)pyridin-2(1H)-one (1.42g) m.p. 284-30 286°C after recrystallisation from ethanol, was prepared according to the method of Example 3(a).

- (b) From 3-cyano-6-(3-bromo-4-methoxyphenyl)pyridin-2(1H)-one (1.22g), the title compound (1.28g) m.p. 292-293°C 35 (decomp) after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b). <sup>1</sup>H

- 53 -

NMR  $\delta$ (DMSO- $d_6$ ) 3.94(s, 3H), 6.90(d, 1H), 7.27(d, 1H),  
7.90(dd, 1H), 8.14(d, 1H) and 8.45(d, 1H).

Example 47

5

6-(3-phenyl-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-  
one (SB 204649)

(a) To a suspension of  
10 tetrakis(triphenylphosphine)palladium (0) (0.5g) in aqueous  
sodium hydrogen carbonate (5.04g in 60ml water), solutions  
of phenylboronic acid (2.65g) in dimethoxyethane (100ml)  
and 3'-bromo-4'-methoxyacetophenone (4.58g) in  
dimethoxyethane (110ml) were added. The mixture was stirred  
15 under reflux for 3 hours cooled to room temperature and  
solvent removed at reduced pressure. The residue was  
partitioned between chloroform (200ml) and water (200ml),  
the organic phase separated dried ( $MgSO_4$ ) and solvent  
removed at reduced pressure. The residue was recrystallised  
20 from ethanol to give 4'-methoxy-3'-phenylacetophenone  
(2.87g) m.p. 92-93°C.

(b) From 4'-methoxy-3'-phenylacetophenone (3.3g), 3-cyano-  
6-(3-phenyl-4-methoxyphenyl)pyridin-2(1H)-one (2.37g) m.p.  
25 288-291°C after recrystallisation from propan-2-ol, was  
prepared according to the method of Example 3(a).

(c) From 3-cyano-6-[(3-phenyl)-4-methoxyphenyl]pyridin-  
2(1H)-one (0.91g), the title compound (0.70g) m.p. 289-  
30 291°C after recrystallisation from  
dimethylformamide/ethanol, was prepared according to the  
method of Example 1(b).  $^1H$  NMR  $\delta$ (DMSO- $d_6$ ) 3.86(s, 3H),  
6.92(d, 1H), 7.28(d, 1H), 7.33-7.48(m, 3H), 7.62(d, 2H), 7.81-  
7.89(m, 2H), 8.45(d, 1H), 11.96(br.s, 1H) and 12.71(br.s, 1H)

35

Example 48

6-[4-Methoxy-3,5-di(E-1-propenyl)phenyl]-3-(5-tetrazolyl)-  
pyridin-2(1H)-one (SB 204788)

5

(a) From 3'-allyl-4'-hydroxyacetophenone (17.6g), 3'-allyl-4'-allyloxyacetophenone (20.7g) isolated as an oil, was prepared according to the method of Example 2(a) using acetone as solvent. <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 2.55(s,3H), 3.44(d,2H),  
10 4.61(m,2H), 5.04-5.46(m,4H), 5.94-6.10(m,2H), 6.86(d,1H), 7.78d,1H) and 7.83(dd,1H).

(b) From 3'-allyl-4'-allyloxyacetophenone (20.5g), 3',5'-diallyl-4'-hydroxyacetophenone (16.3g) m.p. 83-84°C was  
15 prepared according to the method of Example 38(a).

(c) From 3',5'-diallyl-4'-hydroxyacetophenone (16g), 3',5'-diallyl-4'-methoxyacetophenone (17g) isolated as an oil, was prepared according to the method of Example 2(a). <sup>1</sup>H  
20 NMR δ(CDCl<sub>3</sub>) 2.55(s,3H), 3.46(d,4H), 3.77(s,3H), 5.05-5.14(m,4H), 5.91-6.07(m,2H) and 7.69(s,2H).

(d) From 3',5'-diallyl-4'-methoxyacetophenone (8.5g), 3-cyano-6-[4-methoxy-3,5-di(E-1-propenyl)phenyl]pyridin-  
25 2(1H)-one (6.1g) m.p. 248-250°C after trituration with hot ethanol, was prepared according to the method of Example 3(a).

(e) From 3-cyano-6-[4-methoxy-3,5-di(E-1-propenyl)phenyl]pyridin-2(1H)-one (0.46g), the title  
30 compound (0.27g) m.p. 285-287°C (decomp) after recrystallisation from dimethylformamide/water, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.92(d,6H), 3.68(s,3H), 6.49-6.68(m,4H),  
35 7.00(d,1H), 7.89(s,2H) and 8.45(d,1H).

- 55 -

Example 49

6-[3-(E-1-Propenyl)-4-propoxyphenyl]-3-(5-tetrazolyl)-  
pyridin-2(1H)-one. (SB 201433)

5

(a) From 3'-allyl-4'-hydroxyacetophenone (5.28g), 3'-allyl-4'-propoxyacetophenone (6.06g) isolated as an oil was prepared according to the method of Example 2(a). <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 1.07(t,3H), 1.66-1.92(m,2H), 2.55(s,3H),  
10 3.41(d,2H), 3.99(t,2H), 5.04-5.12(m,2H), 5.90-6.06(m,1H), 6.86(d,1H), 7.77(d,1H) and 7.83(dd,1H).

(b) From 3'-allyl-4'-propoxyacetophenone (5.7g), 3-cyano-6-[3-(E-1-propenyl)-4-propoxyphenyl]pyridin-2(1H)-one (2.57g)  
15 m.p. 240-244°C after recrystallisation from butanol, was prepared according to the method of Example 3(a).

(c) From 3-cyano-6-[3-(E-1-propenyl)-4-propoxyphenyl]pyridin-2(1H)-one (1.18g), the title compound  
20 (0.7g) m.p.290-292°C (decomp) after recrystallisation from butanol, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.02(t,3H), 1.73-1.86(m,2H), 1.90(d,3H), 4.04(t,2H), 6.48-6.61(dq,1H), 6.65(d,1H), 6.89(d,1H), 7.11(d,1H), 7.70(dd,1H), 7.97(d,1H) and  
25 8.43(d,1H).

Example 50

6-(3-Bromo-4-methoxy-5-propylphenyl)-3-(5-tetrazolyl)-  
30 pyridin-2(1H)-one. (273/2534)

(a) From 4'-methoxy-3'-propylacetophenone (7.6g), 3'-bromo-4'-methoxy-5'-propylacetophenone (4.8g) isolated as an oil after column chromatography (silica gel, 50%  
35 hexane/dichloromethane eluant) was prepared according to the method of Example 36(a). <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 0.98(t,3H),

- 56 -

1.57-1.73 (m, 2H), 2.56 (s, 3H), 2.67 (t, 2H), 3.87 (s, 3H),  
7.74 (d, 1H) and 7.98 (d, 1H).

(b) From 3'-bromo-4'-methoxy-5'-propylacetophenone (3.4g),  
5 6-(3-bromo-4-methoxy-5-propylphenyl)-3-cyanopyridin-2(1H)-  
one (1.2g) after recrystallisation from ethanol, was  
prepared according to the method of Example 3(a). <sup>1</sup>H NMR  
δ(DMSO-d<sub>6</sub>) 0.94 (t, 3H), 1.57-1.67 (m, 2H), 2.65 (t, 2H),  
3.79 (s, 3H), 6.38 (br.d, 1H), 7.74 (d, 1H), 7.97 (d, 1H) and  
10 8.18 (d, 1H).

(c) From 6-(3-bromo-4-methoxy-5-propylphenyl)-3-  
cyanopyridin-2(1H)-one (0.39g), the title compound (0.17g)  
m.p. 286-287 (decomp) after recrystallisation from ethanol,  
15 was prepared according to the method of Example 1(a). <sup>1</sup>H  
NMR δ(DMSO-d<sub>6</sub>) 0.96 (t, 3H), 1.61-1.70 (m, 2H), 2.67 (t, 2H),  
3.81 (s, 3H), 6.94 (d, 1H), 7.76 (d, 1H), 7.99 (d, 1H) and  
8.45 (d, 1H).

20

Example 51

6-(2-Butylthio-3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-  
2(1H)-one

25 (a) From 2'-bromo-3',5'-diethoxyacetophenone (2.53g), 2'-  
butylthio-3',5'-diethoxyacetophenone (1.96g) after column  
chromatography (silica gel, hexane/dichloromethane 4:1  
eluant) was prepared according to the method of Example  
26(a). <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 0.87 (t, 3H), 1.25-1.65 (m, 10H),  
30 2.59 (s, 3H), 2.76 (t, 2H), 4.02 (q, 2H), 4.08 (q, 2H), 6.33 (d, 1H)  
and 6.46 (d, 1H).

(b) From 2'-butylthio-3',5'-diethoxyacetophenone (1.95g),  
3-cyano-6-(2-butylthio-3,5-diethoxyphenyl)pyridin-2(1H)-one  
35 (0.13g) after recrystallisation from ethanol, was prepared  
according to the method of Example 3(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>)

- 57 -

0.77 (t, 3H), 1.18-1.43 (m, 10H), 2.66 (t, 2H), 4.03-4.18 (m, 4H), 6.27 (d, 1H), 6.59 (d, 1H), 6.71 (d, 1H) and 8.15 (d, 1H).

(c) From 3-cyano-6-(2-butylthio-3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one (0.12g), the title compound (0.08g) m.p. 138-140°C after recrystallisation from ethanol, was prepared according to the method of Example 1(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 0.76 (t, 3H), 1.18-1.43 (m, 10H), 2.64 (t, 2H), 4.05-4.19 (m, 4H), 6.40 (d, 1H), 6.62 (d, 1H), 6.70 (d, 1H), 8.48 (d, 1H) and 12.67 (br.s, 1H).

### Example 52

6-(3-Bromo-4-N,N-dimethylaminophenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one (SB 204789)

(a) From 4'-N,N-dimethylaminoacetophenone (4.9g), 3'-bromo-4'-N,N-dimethylaminoacetophenone (7.0g) was prepared according to the method of Example 36(a). <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 2.53 (s, 3H), 2.91 (s, 6H), 7.03 (d, 1H), 7.83 (dd, 1H) and 8.13 (d, 1H).

(b) From 3'-bromo-4'-N,N-dimethylaminoacetophenone (2.42g), 3-cyano-6-(3-bromo-4-N,N-dimethylaminophenyl)pyridin-2(1H)-one (2.63g) was prepared according to the method of Example 3(a). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 2.82 (s, 6H), 6.82 (d, 1H), 7.22 (d, 1H), 7.79 (dd, 1H), 8.08 (d, 1H), 8.15 (d, 1H) and 12.67 (br.s, 1H).

(c) From 3-cyano-6-(3-bromo-4-N,N-dimethylaminophenyl)pyridin-2(1H)-one (0.8g), the title compound (0.57g) m.p. 275-277°C was prepared according to the method of Example 1(b).

- 58 -

Example 53**6-(3-Acetamido-4-methoxy-5-propylphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one (SB 204790)**

5

(a) From 3'-allyl-4'-hydroxyacetophenone (17.6g), 3'-allyl-4'-benzyloxyacetophenone (23.1g) isolated as an oil was prepared according to the method of Example 2(a) using acetone as solvent. <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 2.55(s,3H), 3.47(d,2H),  
10 5.04-5.11(m,4H), 5.16(s,2H), 5.93-6.09(m,1H), 6.93(d,1H), 7.25-7.41(m,5H), 7.81(s,1H) and 7.82(d,1H).

(b) From 3'-allyl-4'-benzyloxyacetophenone (23g), 6-[4-benzyloxy-3-(E-1-propenyl)phenyl]-3-cyanopyridin-2(1H)-one  
15 (11.2g) m.p. 255-257°C after recrystallisation from dimethylformamide/water, was prepared according to the method of Example 3(a).

(c) A solution of 6-[4-benzyloxy-3-(E-1-propenyl)phenyl]-3-cyanopyridin-2(1H)-one (6.8g) in dimethylformamide (20ml)  
20 containing dimethylformamide dimethyl acetal (4.76g) was heated at 120°C for 6 hours. The mixture was diluted with ethyl acetate (200ml), washed with water (6 x 100ml), dried (MgSO<sub>4</sub>) and solvent removed at reduced pressure. The  
25 residue was column chromatographed (silica gel, hexane/dichloromethane 1:1 eluant) to give 6-[4-benzyloxy-3-(E-1-propenyl)phenyl]-3-cyano-2-methoxypyridine (6g) m.p. 124-125°C after recrystallisation from ethanol.

30 (d) A suspension of 6-[4-benzyloxy-3-(E-1-propenyl)phenyl]-3-cyano-2-methoxypyridine (1.78g) in ethanol (250ml) containing 10% palladium/charcoal (0.2g) was hydrogenated at 50 p.s.i until the calculated quantity of hydrogen had been absorbed. The mixture was filtered (celite pad) and  
35 solvent removed at reduced pressure. The residue was column chromatographed (silica gel, hexane/dichloromethane 1:1 - 2% ethanol/dichloromethane eluant) to give 3-cyano-6-(4-

- 59 -

hydroxy-3-propylphenyl)-2-methoxypyridine (1.0g).  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.01(t,3H), 1.65-1.74(m,2H), 2.66(t,2H), 4.15(s,3H) 5.19(s,1H), 6.86(d,1H), 7.35(d,1H) and 7.81-7.87(m,3H).

5

(e) To a stirred suspension of 6-(4-hydroxy-3-propylphenyl)-3-cyano-2-methoxypyridine (1.88g) in sulpholane (3ml) a solution of nitronium tetrafluoroborate in sulpholane (0.5M, 16ml) was added over 5 minutes with ice cooling. The solution obtained was stirred for 5 hours, additional nitronium tetrafluoroborate (0.5M in sulpholane, 2ml) added and stirring continued for a further 3 hours. The solution was diluted with diethyl ether (100ml) washed with water (8 x 100ml), dried ( $\text{MgSO}_4$ ) and solvent removed at reduced pressure. The residue was recrystallised from ethanol to give 3-cyano-6-(4-hydroxy-3-nitro-5-propylphenyl)-2-methoxypyridine (1.75g) m.p. 160-162°C.

(f) From 3-cyano-6-(4-hydroxy-3-nitro-5-propylphenyl)-2-methoxypyridine (1.57g), 3-cyano-6-(4-methoxy-3-nitro-5-propylphenyl)-2-methoxypyridine (1.53g) m.p. 150-152°C was prepared according to the method of Example 2(a) using acetone/dimethylformamide (1:1) as reaction solvent.  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.03(t,3H), 1.67-1.81(m,2H), 2.77(t,2H), 3.95(s,3H), 4.17(s,3H), 7.42(d,1H), 7.96(d,1H), 8.07(d,1H) and 8.35(d,1H).

(g) A suspension of 3-cyano-6-(4-methoxy-3-nitro-5-propylphenyl)-2-methoxypyridine (1.4g) in ethanol (100ml) containing 10% palladium/charcoal (200mg) was treated with hydrogen at 50 p.s.i until hydrogen uptake was complete. The mixture was filtered (celite pad) and solvent removed from the filtrate at reduced pressure. The residue was dissolved in dichloromethane (10ml) containing triethylamine (1.01g) added followed by the addition of acetic anhydride (0.61g) over 5 minutes. The reaction mixture was stirred for 15 hours, diluted with

- 60 -

dichloromethane (100ml) and washed with 2N hydrochloric acid (2 x 50ml) and with water (50ml). After drying ( $\text{MgSO}_4$ ), solvent was removed at reduced pressure to give after recrystallisation from ethanol 6-(3-acetamido-4-methoxy-5-propylphenyl)-3-cyano-2-methoxypyridine (1.04g) m.p. 174-175°C.

(h) From 6-(3-acetamido-4-methoxy-5-propylphenyl)-3-cyano-2-methoxypyridine (0.7g), 6-(3-acetamido-4-methoxy-5-propylphenyl)-3-cyanopyridin-2(1H)-one (0.48g) m.p. 247-249°C was prepared according to the method of Example 37(c).  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.02 (t, 3H), 1.68-1.83 (m, 2H), 2.27 (s, 3H), 2.78 (t, 2H), 3.83 (s, 3H), 6.65 (d, 1H), 7.49 (d, 1H), 7.80 (br. s, 1H), 7.90 (d, 1H) and 8.62 (d, 1H).

(i) From 6-(3-acetamido-4-methoxy-5-propylphenyl)-3-cyanopyridin-2(1H)-one (0.4g), the title compound (0.25g) m.p. 239-241°C after recrystallisation from ethanol, was prepared according to the method of Example 1(b)

#### Example 54

6-[3-Methoxymethyl-4-methoxy-5-(E-1-propenyl)phenyl]-3-(5-tetrazolyl)pyridin-2(1H)-one (273/2588)

25

(a) From 3-cyano-6-[4-methoxy-3,5-di(E-1-propenyl)phenyl]pyridin-2(1H)-one (4.59g), 3-cyano-6-[4-methoxy-3,5-di(E-1-propenyl)phenyl]-2-methoxypyridine (4.1g) m.p. 145°C was prepared according to the method of Example 53(c).  $^1\text{H}$  NMR  $\delta(\text{DMSO}-d_6)$  1.93 (d, 6H), 3.67 (s, 3H), 4.11 (s, 3H), 6.42-6.56 (m, 2H), 6.66 (d, 2H), 7.87 (d, 1H), 8.15 (s, 2H) and 8.30 (d, 1H).

30

(b) To an ice cooled suspension of 3-cyano-6-[4-methoxy-3,5-di(E-1-propenyl)phenyl]-2-methoxypyridine (1.6g) in acetone/water (9:1, 100ml) N-methylmorpholine-N-oxide (0.63g) and osmium tetroxide (2.5% w/w solution in tert-

35

- 61 -

butanol, 0.4ml) were added. The mixture was stirred with ice cooling for 1 hour and at room temperature for 1 hour. Additional N-methylmorpholine-N-oxide (0.1g) was added and stirring continued for an additional 1 hour. The solution  
5 was quenched with 5% sodium metabisulphite (5ml) and solvent removed at reduced pressure. The residue was dissolved in ethyl acetate (200ml), washed with water (2 x 100ml), dried ( $\text{MgSO}_4$ ) and solvent removed at reduced pressure. Column chromatography (silica gel,  
10 dichloromethane-5% ethanol/dichloromethane eluant) gave 3-cyano-6-[3-[1-(1,2-dihydroxypropyl)]-4-methoxy-5-(E-1-propenyl)phenyl]-2-methoxypyridine (0.99g).  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.17(d,3H), 1.97(d,3H), 2.5(br.s,1H), 2.98(br.s,1H), 3.82(s,3H), 3.94-4.05(m,1H), 4.16(s,3H), 4.77(d,1H), 6.30-  
15 6.42(m,1H), 6.66(d,1H), 7.41(d,1H), 7.90(d,1H), 7.93(d,1H) and 8.08(d,1H).

(c) To a solution of 3-cyano-6-[3-[1-(1,2-dihydroxypropyl)]-4-methoxy-5-(E-1-propenyl)phenyl]-2-  
20 methoxypyridine (0.99g) in tetrahydrofuran (20ml) a solution of sodium metaperiodate (0.64g) in water (3ml) was added. The mixture was stirred for 2 hours, additional sodium metaperiodate (0.1g) in water (2ml) added and stirring continued for a further 2 hours. The mixture was filtered,  
25 diluted with ethyl acetate (100ml), washed with water (2 x 50ml), dried ( $\text{MgSO}_4$ ) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane- 5% ethanol/dichloromethane eluant) to give 3-cyano-6-[3-formyl-4-methoxy-5-(E-1-propenyl)phenyl]-  
30 2-methoxypyridine (0.7g) m.p. 174°C.  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  2.00(d,3H), 3.93(s,3H), 4.18(s,3H), 6.38-6.53(m,1H), 6.69(d,1H), 7.47(d,1H), 7.94(d,1H), 8.33(d,1H), 8.41(d,1H) and 10.44(1H).

35 (d) A solution of 3-cyano-6-[3-formyl-4-methoxy-5-(E-1-propenyl)phenyl]-2-methoxypyridine (0.65g) in ethanol (10ml) was treated with sodium borohydride (100mg) in

- 62 -

portions over 30 minutes. The solution was stirred for a further 2 hours, solvent removed at reduced pressure, the residue dissolved in ethyl acetate (100ml), washed with water (2 x 50ml), dried ( $\text{MgSO}_4$ ) and solvent removed at reduced pressure. The residue was dissolved in dimethyl sulphoxide (5ml), potassium hydroxide (0.56g, crushed pellets) added, followed by iodomethane (0.6g) and the mixture stirred for 30 minutes. After diluting with ethyl acetate (100ml) the reaction mixture was washed with water (6 x 50ml), dried ( $\text{MgSO}_4$ ) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 40% hexane/dichloromethane - dichloromethane) to give 3-cyano-6-[3-methoxymethyl-4-methoxy-5-(E-1-propenyl)phenyl]-2-methoxypyridine (0.54g) m.p. 81-82°C.  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.96(d,3H), 3.47(s,3H), 3.79(s,3H), 4.17(s,3H), 4.56(s,2H), 6.306.42(m,1H), 6.70(d,1H), 7.42(d,1H), 7.88(d,1H), 7.92(d,1H) and 8.10(d,1H).

(e) From 3-cyano-6-[3-methoxymethyl-4-methoxy-5-(E-1-propenyl)phenyl]-2-methoxypyridine (0.54g), 3-cyano-6-[3-methoxymethyl-4-methoxy-5-(E-1-propenyl)phenyl]pyridin-2(1H)-one (0.33g) m.p.188-190°C after column chromatography (silica gel, dichloromethane - 2.5% ethanol/dichloromethane eluant), was prepared according to the method of Example 37(c).  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$  1.99(d,3H), 3.49(s,3H), 3.81(s,3H), 4.60(s,2H), 6.46-6.70(m,3H), 7.72(d,1H), 7.85(d,1H), 7.91(d,1H) and 12.89(br.s,1H).

(f) From 3-cyano-6-[3-methoxymethyl-4-methoxy-5-(E-1-propenyl)phenyl]pyridin-2(1H)-one (0.3g) the title compound (0.22g) m.p. 245-246°C after recrystallisation from ethanol, was prepared according to the method of Example 1(b).  $^1\text{H}$  NMR  $\delta(\text{DMSO}-d_6)$  1.92(d,3H), 3.61(s,3H), 3.83(s,3H), 4.81(s,2H), 6.26-6.44(m,1H), 6.68(d,1H), 6.88(d,1H), 7.73(d,1H), 8.04(d,1H), 8.75(d,1H)

- 63 -

Example 55

6-[3-(E-2-Carbamoylethenyl)-4-methoxy-5-(E-1-propenyl)phenyl]-3-(5-tetrazolyl)pyridin-2-(1H)-one  
5 (273/2602)

(a) Triethylphosphonoacetate (0.9g) was added dropwise to a suspension of sodium hydride (0.18g, 50% in oil) in tetrahydrofuran (10ml). When gas evolution had ceased a  
10 solution of 3-cyano-6-[3-formyl-4-methoxy-5-(E-1-propenyl)phenyl]-2-methoxypyridine in tetrahydrofuran (10ml) was added and the mixture stirred for 4 hours. Ethanol (10ml) and 2N sodium hydroxide (10ml) were added and the mixture boiled for 2 hours. Solvent was removed at  
15 reduced pressure, the residue dissolved in water and acidified with 2N hydrochloric acid. The precipitate was collected by filtration to give 3-cyano-6-[3-(E-2-carboxylatoethenyl)-4-methoxy-5-(E-1-propenyl)phenyl]-2-methoxypyridine (0.9g). <sup>1</sup>H NMR δ(CDCl<sub>3</sub>) 1.94(d, 3H),  
20 3.73(s, 3H), 4.14(s, 3H), 6.50-6.62(m, 1H), 6.69(d, 1H), 6.78(d, 1H), 7.82(1H), 7.99(d, 1H) and 8.33-8.42(m, 3H).

(b) Oxalyl chloride (0.76g) was added over 5 minutes to an ice cooled suspension of 3-cyano-6-[3-(E-2-carboxylatoethenyl)-4-methoxy-5-(E-1-propenyl)phenyl]-2-methoxypyridine in dichloromethane (20ml) containing  
25 dimethylformamide (0.1ml). When gas evolution had ceased (4 hours) solvent was removed at reduced pressure and the residue redissolved in dichloromethane (20ml). To the ice  
30 cooled solution ammonium hydroxide (10ml, SG 0.88) was added and the solution stirred at 0°C for 30 minutes and at room temperature for 30 minutes. The precipitated solid was collected by filtration and recrystallised twice from ethanol to give 3-cyano-6-[3-(E-2-carbamoylethenyl)-4-methoxy-5-(E-1-propenyl)phenyl]pyridin-2(1H)-one (0.4g)  
35 m.p. 245-246°C. <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub>) 1.94(d, 3H), 3.72(s, 3H), 4.14(s, 3H), 6.49-6.62(m, 1H), 6.66(d, 1H), 6.80(d, 1H),

- 64 -

7.19 (br.s, 1H), 7.62 (br.s, 1H), 7.62 (d, 1H), 7.89 (d, 1H),  
8.27 (d, 1H), 8.29 (d, 1H) and 8.34 (d, 1H).

(c) From 3-cyano-6-[3-(E-2-carbamoylethenyl)-4-methoxy-5-  
5 (E-1-propenyl)phenyl]-2-methoxypyridine (0.35g), 3-cyano-6-  
[3-(E-2-carbamoylethenyl)-4-methoxy-5-(E-1-  
propenyl)phenyl]pyridin-2(1H)-one (0.2g) m.p. >300°C after  
recrystallisation from dimethylformamide/ethanol/water, was  
prepared according to the method of Example 37(c). <sup>1</sup>H NMR  
10 δ(DMSO-d<sub>6</sub>) 1.93 (d, 3H), 3.71 (s, 3H), 6.51-6.71 (m, 2H),  
6.91 (br.d, 1H), 7.21 (br.s, 1H), 7.61 (d, 1H), 7.62 (br.s, 1H),  
7.93 (s, 1H), 7.99 (s, 1H), 8.20 (d, 1H) and 12.78 (br.s, 1H).

(d) From 3-cyano-6-[3-(E-2-carbamoylethenyl)-4-methoxy-5-  
15 (E-1-propenyl)phenyl]pyridin-2(1H)-one (0.16g), the title  
compound (0.08g) m.p. 292-294°C (decomp) after  
recrystallisation from dimethylformamide/ethanol/water, was  
prepared according to the method of Example 1(b) <sup>1</sup>H NMR  
δ(DMSO-d<sub>6</sub>) 1.94 (d, 3H), 3.73 (s, 3H), 6.55-6.72 (m, 2H),  
20 6.83 (d, 1H), 7.00 (d, 1H), 7.23 (br.s, 1H), 7.62 (d, 1H),  
7.66 (br.s, 1H), 7.99 (d, 1H) and 8.48 (d, 1H).

#### Example 56

25 **6-(3-Cyclopropylmethyloxy-4-methoxyphenyl)pyridin-2(1H)-one**

(a) From 3'-hydroxy-4'-methoxyacetophenone (3.32g), 3'-  
cyclopropylmethyloxy-4'-methoxyacetophenone (4.34g) was  
prepared according to the method of Example 2(a). <sup>1</sup>H NMR  
30 δ(CDCl<sub>3</sub>) 0.34-0.40 (m, 2H), 0.63-0.70 (m, 2H), 1.28-1.43 (m, 1H),  
2.56 (s, 3H), 3.91 (d, 2H), 3.95 (s, 3H), 6.89 (d, 1H), 7.50 (d, 1H)  
and 7.56 (dd, 1H).

(b) From 3'-cyclopropylmethyloxy-4'-methoxyacetophenone  
35 (3.55g), 3-cyano-6-(3-cyclopropylmethyloxy-4-  
methoxyphenyl)pyridin-2(1H)-one (1.30g) m.p. 241-242°C

- 65 -

after recrystallisation from butanol was prepared according to the method of Example 3(a).

- (c) From 3-cyano-6-(3-cyclopropylmethoxy-4-methoxyphenyl)pyridin-2(1H)-one (0.89g), the title compound (0.67g) m.p. 296-297°C (decomp) after recrystallisation from butanol, was prepared according to the method of Example 1(b).  $^1\text{H}$  NMR  $\delta$ (DMSO- $d_6$ ) 0.32-0.38(m, 2H), 0.57-0.66(m, 2H), 1.22-1.37(m, 1H), 3.85(s, 1H), 3.94(d, 2H), 6.88(d, 1H), 7.10(d, 1H), 7.39-7.48(m, 2H), 8.43(d, 1H) and 12.56(br.s, 1H).

#### Example 57

- 6-(2-methoxy-4-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

- (a) From 2'-4'-dihydroxyacetophenone (50g), 2'-hydroxy-4'-propoxyacetophenone (6g) was prepared according to the method of Example 2(a), using bromopropane (40g) and acetone as solvent.  $^1\text{H}$  NMR  $\delta$ (DMSO- $d_6$ ) 0.93(t, 3H), 1.61-1.72(m, 2H), 2.38(s, 3H), 3.75(t, 2H), 5.61(dd, 1H), 5.80(d, 1H) and 7.40(d, 1H).

- (b) From 2'-hydroxy-4'-propoxyacetophenone (6g), 2'-methoxy-4'-propyloxyacetophenone (5.18g) was prepared according to the method of Example 2(a).  $^1\text{H}$  NMR  $\delta$ (CDCl<sub>3</sub>) 1.05(t, 3H), 1.74-1.91(m, 2H), 2.57(s, 3H), 3.89(s, 3H), 3.97(t, 2H), 6.46-6.53(m, 2H) and 7.80(d, 1H).

- (c) From 2'-methoxy-4'-propoxyacetophenone (5g), 3-cyano-6-(2-methoxy-4-propoxyphenyl)pyridin-2(1H)-one (0.38g) m.p. 186-188°C after trituration with diethyl ether was prepared according to the method of Example 3(a).  $^1\text{H}$  NMR  $\delta$ (DMSO- $d_6$ ) 0.99(t, 3H), 1.72-1.81(m, 2H), 3.82(s, 3H), 4.02(s, 2H), 6.47(d, 1H), 6.61-6.67(m, 2H), 7.39(d, 1H) and 8.11(d, 1H).

- 66 -

(d) From 3-cyano-6-(2-methoxy-4-propoxyphenyl)pyridin-2(1H)-one (0.36g), the title compound (0.04g) m.p. >300°C after recrystallisation from ethanol and trituration with diethyl ether, was prepared according to the method of Example 1(b). <sup>1</sup>H NMR δ(DMSO-d<sub>6</sub> at 370K) 1.00(t,3H), 1.69-1.82(m,2H), 3.83(s,3H), 4.02(t,2H), 6.61-6.66(m,2H), 6.98(unresolved,1H), 7.55(unresolved,1H) and 8.44(unresolved,1H).

10

Example X

Pharmaceutical compositions for oral administration are prepared by combining the following :

15

% w/w

6-(3-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one	0.5	3.0	7.14
---	-----	-----	------

20

2% w/w Soya lecithin in soya bean oil	90.45	88.2	84.41
---------------------------------------	-------	------	-------

Hydrogenated vegetable shortening and beeswax	9.05	8.8	8.45
---	------	-----	------

25

The formulations are then filled into individual soft gelatin capsules.

Example Y

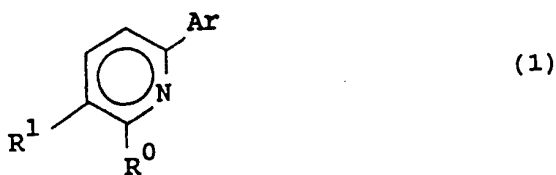
30

A pharmaceutical composition for parenteral administration is prepared by dissolving the title compound of Example 23 (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

35

Claims

1. A compound of the formula (1) :



or a pharmaceutically acceptable salt thereof, wherein :

R<sup>0</sup> is OH or a bioprecursor thereof,

R<sup>1</sup> is 5-tetrazolyl, or a bioprecursor thereof and

Ar is phenyl substituted by one to three groups independently selected from C<sub>1-6</sub>alkyl,

C<sub>2-6</sub>alkenyl, C<sub>1-6</sub>alkoxy, C<sub>3-6</sub>alkenyloxy, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkoxy, C<sub>1-6</sub>alkylthio, phenyl, phenylthio, benzyloxy, C<sub>1-6</sub>polyfluoroalkyl, C<sub>1-6</sub>polyfluoroalkoxy, halo, NR<sub>2</sub>, or NHCOR wherein R is H or C<sub>1-6</sub>alkyl, or -X(CH<sub>2</sub>)<sub>n</sub>Y- attached to adjacent carbon atoms of the phenyl ring wherein X and Y are independently CH<sub>2</sub> or O and n is 1 to 3, wherein said C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>1-6</sub>alkoxy groups can be independently substituted by OH, C<sub>1-6</sub>alkoxy, C<sub>3-6</sub>cycloalkyl, NR<sub>2</sub>, CO<sub>2</sub>R or CONR<sub>2</sub>; with the proviso that Ar is not phenyl monosubstituted by 2-C<sub>1-6</sub>alkoxy.

2. A compound according to claim 1 wherein R<sup>0</sup> is OH or OR<sup>2</sup> in which R<sup>2</sup> is C<sub>1-4</sub>alkyl, arylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkanoyl, arylsulphonyl or C<sub>1-4</sub>alkylsulphonyl.

- 68 -

3. A compound according to claim 1 or 2 wherein Ar is phenyl mono-substituted by a group as defined in claim 1.

5           4. A compound according to claim 1 or 2 wherein Ar is phenyl di-substituted by any two groups as defined in claim 1.

10           5. A compound according to claim 1 or 2 wherein Ar is phenyl trisubstituted by any three groups as defined in claim 1.

6. A compound according to claim 1 which is :

15   6-(3-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(3-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(3-butoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
20   6-(3-benzyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(3-bromophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
25   6-(3-trifluoromethyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(3-ethylphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(4-butoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
30   6-(4-isobutylphenyl)pyridin-2(1H)-one,  
6-(4-biphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
35   6-(4-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

- 69 -

6-(4-methoxy-3-propoxyphenyl)-3-(5-tetrazolyl)pyridin-  
2(1H)-one,

5 6-(3,4-methylenedioxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-  
one,

6-(3,4-dichlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

10 6-(3,5-dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

15 6-(3,5-dibromophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(2,4-dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

20 6-(2,5-dipropoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(2,3,4-trichlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-[6-(1,2,3,4-tetrahydronaphthyl)]-3-(5-tetrazolyl)pyridin-  
2(1H)-one,

25 6-(3-chlorophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(3-phenylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

30 3,4-dimethoxyphenyl-3-(5-tetrazolyl)pyridin-2(1H)-one,  
6-(3-methylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

35 6-(3-butylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

- 70 -

6-(3,4-di-n-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

5 6-(2,3-di-n-propoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(3-cyclopentyloxy-4-methoxyphenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one,

10 6-(3-ethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

15 6-(3,5-dimethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(2-butylthiophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

20 6-(3-allyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(4-methoxy-2-pentyloxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

25 6-(3-iso-butoxy-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

30 6-(2-bromo-3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(5-bromo-4-methoxy-2-pentyloxyphenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one,

35 6-(2-allyl-4-methoxy-3-propoxyphenyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one,

- 71 -

- 6-[3-(E-1-propenyl)-4-methoxyphenyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 5 6-(4-methoxy-3-propoxyphenyl)-3-[5-(1-pivaloyloxymethyl)-tetrazolyl]pyridin-2(1H)-one,
- 6-(4-methoxy-3-propoxyphenyl)-3-[5-(2-pivaloyloxymethyl)-tetrazolyl]pyridin-2(1H)-one,
- 10 6-[3-ethoxy-5-(2-methoxyethoxy)phenyl]-3-(5-tetrazolyl)-pyridin-2(1H)-one,
- 6-[3-(2,2-dimethylpropyloxy)-4-methoxyphenyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 15 6-(3-ethoxy-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3-propionamidophenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 20 6-(4-methoxy-3-propylphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 25 6-(3-bromo-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 6-(3-phenyl-4-methoxyphenyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,
- 30 6-[4-methoxy-3,5-di(E-1-propenyl)phenyl]-3-(5-tetrazolyl)-pyridin-2(1H)-one,
- 6-[3-(E-1-propenyl)-4-propoxyphenyl]-3-(5-tetrazolyl)-pyridin-2(1H)-one,
- 35

- 72 -

6-(3-bromo-4-methoxy-5-propylphenyl)-3-(5-tetrazolyl)-  
pyridin-2-(1H)-one,

5 6-(2-butylthio-3,5-diethoxyphenyl)-3-(5-tetrazolyl)pyridin-  
2(1H)-one,

6-(3-bromo-4-N,N-dimethylaminophenyl)-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,

10 6-(3-acetamido-4-methoxy-5-propylphenyl)-3-(5-tetrazolyl)-  
pyridin-2(1H)-one,

15 6-[3-methoxymethyl-4-methoxy-5-(E-1-propenyl)phenyl]-3-(5-  
tetrazolyl)pyridin-2(1H)-one,

6-[3-(E-2-carbamoylethenyl)-4-methoxy-5-(E-1-propenyl)-  
phenyl]-3-(5-tetrazolyl)pyridin-2-(1H)-one, or

20 6-(3-cyclopropylmethoxy-4-methoxyphenyl)pyridin-2(1H)-  
one

or a pharmaceutically acceptable salt thereof.

25 7. A compound according to any one of claims 1 to 6  
for use as a medicament.

8. A pharmaceutical composition which comprises a  
compound according to any one of claims 1 to 6 and a  
pharmaceutically acceptable carrier.

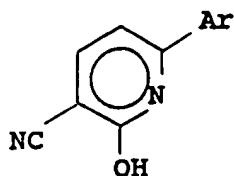
30

- 73 -

9. A process for preparing a compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof which process comprises reacting a compound of the formula (2) :

5

10



(2)




15 wherein Ar is as hereinbefore defined with an azide salt, and optionally thereafter :

- forming a bioprecursor of  $R^0$  and/or  $R^1$
- 20 • forming a pharmaceutically acceptable salt.

10. A compound of the formula (2) as defined in claim 9.

25

## International Application No

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5                      C 07 D 401/04                      A 61 K 31/44														
<b>II. FIELDS SEARCHED</b> <div style="text-align: center;">Minimum Documentation Searched<sup>7</sup></div> <table border="1" style="width: 100%;"> <tr> <th style="width: 20%;">Classification System</th> <th style="width: 80%;">Classification Symbols</th> </tr> <tr> <td>Int.Cl.5</td> <td>C 07 D 401/00                      A 61 K 31/00</td> </tr> </table> <div style="text-align: center;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched<sup>8</sup></div>			Classification System	Classification Symbols	Int.Cl.5	C 07 D 401/00                      A 61 K 31/00								
Classification System	Classification Symbols													
Int.Cl.5	C 07 D 401/00                      A 61 K 31/00													
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b> <table border="1" style="width: 100%;"> <tr> <th style="width: 10%;">Category *</th> <th style="width: 70%;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%;">Relevant to Claim No.<sup>13</sup></th> </tr> <tr> <td>X</td> <td>EP,A,0347027 (SMITH KLINE &amp; FRENCH LABORATORIES LTD) 20 December 1989, see example 5 ---</td> <td>1,7,8</td> </tr> <tr> <td>A</td> <td>Chemical Pharmacological Bulletin, volume 30, no. 12, 1982 (Tokyo, JP) Y. Honma et al.: "Studies on antiallergic agents. I. Phenyl-substituted heterocycles with a 5-tetrazolyl or N-(5-tetrazolyl)carbamoyl group", pages 4314-4324, see page 4318, compound 57 ---</td> <td>1,7,8</td> </tr> <tr> <td>X</td> <td>Registry Handbook, number section, 1987, supplement, registry numbers 107982-26-3 through 110170-82-6, Chemical Abstracts Service, (Columbus, Ohio, US) see page 1208, registry numbers 107487-93-4; 107487-94-5, 107487-95-6; 107488-00-6; 107488-01-7; 107488-02-8 --- -/-</td> <td>10</td> </tr> </table>			Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	EP,A,0347027 (SMITH KLINE & FRENCH LABORATORIES LTD) 20 December 1989, see example 5 ---	1,7,8	A	Chemical Pharmacological Bulletin, volume 30, no. 12, 1982 (Tokyo, JP) Y. Honma et al.: "Studies on antiallergic agents. I. Phenyl-substituted heterocycles with a 5-tetrazolyl or N-(5-tetrazolyl)carbamoyl group", pages 4314-4324, see page 4318, compound 57 ---	1,7,8	X	Registry Handbook, number section, 1987, supplement, registry numbers 107982-26-3 through 110170-82-6, Chemical Abstracts Service, (Columbus, Ohio, US) see page 1208, registry numbers 107487-93-4; 107487-94-5, 107487-95-6; 107488-00-6; 107488-01-7; 107488-02-8 --- -/-	10
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>												
X	EP,A,0347027 (SMITH KLINE & FRENCH LABORATORIES LTD) 20 December 1989, see example 5 ---	1,7,8												
A	Chemical Pharmacological Bulletin, volume 30, no. 12, 1982 (Tokyo, JP) Y. Honma et al.: "Studies on antiallergic agents. I. Phenyl-substituted heterocycles with a 5-tetrazolyl or N-(5-tetrazolyl)carbamoyl group", pages 4314-4324, see page 4318, compound 57 ---	1,7,8												
X	Registry Handbook, number section, 1987, supplement, registry numbers 107982-26-3 through 110170-82-6, Chemical Abstracts Service, (Columbus, Ohio, US) see page 1208, registry numbers 107487-93-4; 107487-94-5, 107487-95-6; 107488-00-6; 107488-01-7; 107488-02-8 --- -/-	10												
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents : <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>														
<b>IV. CERTIFICATION</b> <table border="1" style="width: 100%;"> <tr> <td style="width: 50%;">           Date of the Actual Completion of the International Search   <div style="text-align: center;">27-12-1991</div> </td> <td style="width: 50%;">           Date of Mailing of this International Search Report   <div style="text-align: center;">12.02.92</div> </td> </tr> <tr> <td>           International Searching Authority   <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> </td> <td>           Signature of Authorized Officer    <div style="text-align: center;">Natalie Weinberg</div> </td> </tr> </table>			Date of the Actual Completion of the International Search  <div style="text-align: center;">27-12-1991</div>	Date of Mailing of this International Search Report  <div style="text-align: center;">12.02.92</div>	International Searching Authority  <div style="text-align: center;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer  <div style="text-align: center;">Natalie Weinberg</div>								
Date of the Actual Completion of the International Search  <div style="text-align: center;">27-12-1991</div>	Date of Mailing of this International Search Report  <div style="text-align: center;">12.02.92</div>													
International Searching Authority  <div style="text-align: center;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer  <div style="text-align: center;">Natalie Weinberg</div>													

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

(CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Chemical Abstracts, volume 95, no. 9, 1981, (Columbus, Ohio, US) see page 788, abstract 80943j, & BE, A, 885484 (MEIJI SEIKA KAISHA, LTD) 2 February 1981 ---	10
X	Chemical Abstracts, volume 86, no. 17, 1977 (Columbus, Ohio, US) J. Liebscher et al.: "Chemistry of activated vinyl halides. Synthesis and reaction behavior of 3-(beta-chlorovinyl)acrylonitriles", see page 513, abstract 120947m, & J. Prakt. Chem., 1976, 318(5), 705-30 -----	10

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers \_\_\_\_\_ because they relate to subject matter not required to be searched by this Authority, namely: \_\_\_\_\_
2. ☒ Claim numbers 10 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  

Claim numbers 10: Claim 10 is so broad that a complete search was not possible for economical reasons
3. ☐ Claim numbers \_\_\_\_\_ because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: \_\_\_\_\_
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: \_\_\_\_\_
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## SA 51749

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 21/01/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0347027	20-12-89	AU-B- 616001	17-10-91
		AU-A- 3309689	26-10-89
		JP-A- 1311067	15-12-89
-----			